

Preface to “A PK/PBPK MODEL QUALITY ASSURANCE ASSESSMENT FOR THE TSCA WORKPLAN RISK ASSESSMENT OF N-Methylpyrrolidone”

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Poet *et al.* (2010) developed a PBPK model to reduce uncertainty associated with extrapolating findings from animal toxicity studies to humans. These authors initially developed the model for adult non-pregnant rats and then extrapolated it to pregnancy. The U.S. EPA regularly reviews not only the primary publications describing PBPK models, but performs a quality assurance (QA) review, as described by (McLanahan et al., 2012). Since the model as described by Poet et al. (2010) appeared to be of sufficient scientific quality, the model code was obtained from the principle author, Dr. Torka Poet. The QA process involves checking that the published tables and figures can be reproduced, that the parameters used in the code match those listed in the publication (or at a minimum, are consistent between model simulations and appropriate for the chemical and animal species and/or humans being simulated), and that the equations in the code are correct and match those listed or indicated in the published paper. This review has been conducted by members of the U.S. EPA National Center for Environmental Assessment (NCEA) Pharmacokinetics Workgroup (PKWG), with technical support through an external contract. The contractor's report and further details from the PKWG NMP team lead (Paul Schlosser) follow.

The initial QA review conducted in the fall of 2012 found several code errors and parameter inconsistencies in the model and the EPA was not able to reproduce all of the figures in Poet et al. (2010) as well as should be possible. At that point the model was not considered to be of sufficient quality for use in a risk assessment. Subsequently Dr. Torka Poet corrected the model errors originally found by the U.S. EPA and created a set of scripts to aid in reproducing her results (for the NMP Producers Group). As these changes substantially changed some of the model predictions, the revised model results were described in a report that was submitted to the U.S. EPA in April, 2013.

Overall quality: The U.S. EPA then treated this revised model report (Poet, 2013) and code as a new publication and again conducted a QA review. Several more coding and parameter errors were found, as described below in this preface, in the contractor's report which follows, and in EPA's appendix to that report. In this case, however, correcting the errors caused only modest changes in the model predictions (fits to data) used to calibrate the model and determine its suitability for risk prediction, subsequent to the changes and corrections described here, in the QA report, and appendix. Since the fits of the model to the various data sets evaluated appears adequate and the parameter values are appropriate and consistent, the model is now deemed to be of sufficient quality for use in this risk assessment.

Dermal absorption of NMP vapor: One parameter inconsistency that results in differences in predictions for human exposure scenarios is the assumed surface area (SA) of skin through which vapor can be absorbed. The human model calibration for inhalation was conducted by Poet (2013) with a SA of 6700 cm², presumed to be face, neck, lower arms, and hands, through which vapor was absorbed, accounting for about 45% of the uptake when exposure is by inhalation only. Since these skin areas would also be exposed to vapors for individuals working with NMP, the model code and parameter files were revised to

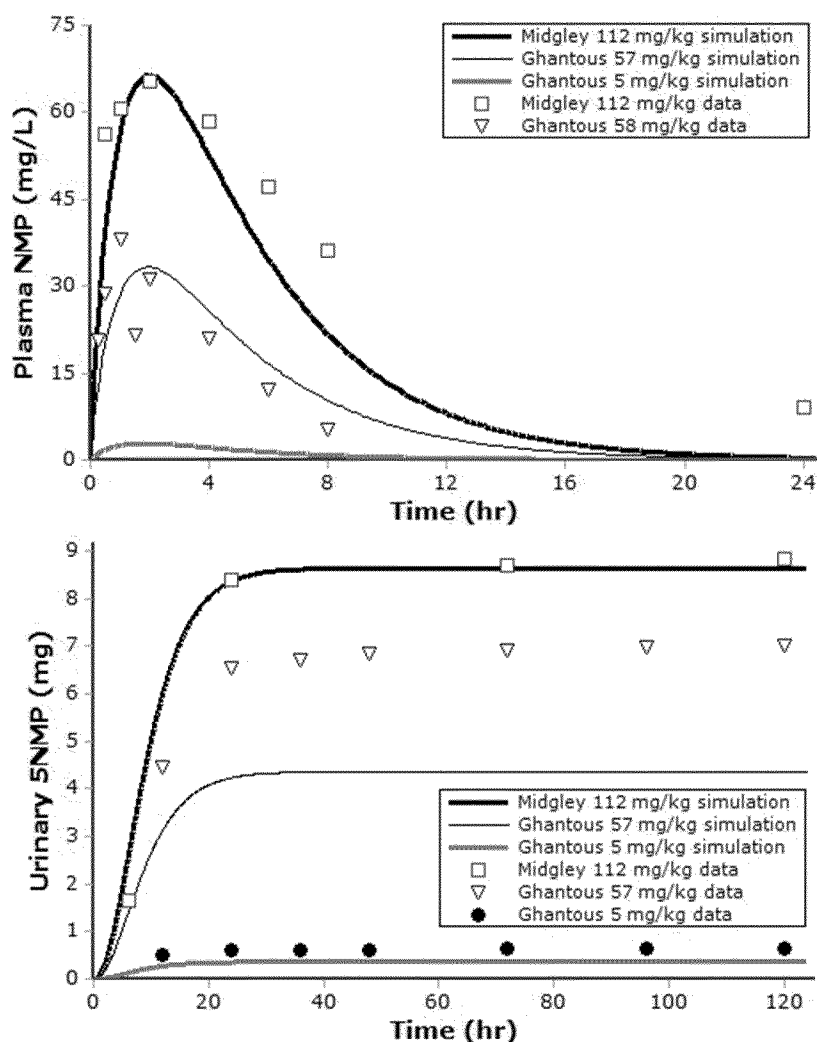
include this route and SA as base assumptions for human exposures, which can occur simultaneous with dermal liquid absorption.

Oral absorption kinetics in rats: While the oral exposure is not of concern for human workplace and residential scenarios being evaluated by OPPT, the rat PBPK model includes oral dosimetry and calibration to rat oral data was shown by Poet et al. (2010). In order to evaluate possible internal dose metrics for their ability to predict developmental effects, oral bioassay data for rats is also evaluated in the dose-response analysis. Hence the ability of the rat model to correctly predict internal doses after oral exposure is also important. However, since this calibration was not carried forward from Poet et al. (2010) to Poet (2013), it was not evaluated in the contractor's report which follows.

When the otherwise revised model was tested by the U.S. EPA for its ability to reproduce the oral absorption kinetics shown in Figure 5 or Poet et al. (2010) for rats, an error in the coding (revised version provided with Poet (2013)) gave a significant discrepancy between the predictions with the revised model and that figure. In particular, the total mass of NMP available for oral uptake was not reduced to reflect the oral bioavailability (FRACOR = 68%) reported by Poet et al. (2010) and instead the rate constant for absorption, KAS, was effectively reduced by this extent. Since any material deposited in the model's stomach lumen compartment is eventually absorbed, irrespective of the value of KAS, the effective bioavailability was therefore erroneously treated as being 100%. When the code was corrected to reduce the mass deposited to the stomach lumen compartment to 68% and KAS also reduced to 0.92/h (68% of the value in the provided code, 1.36/h), and the incorrect multiplication of KAS and FRACOR removed from the code, fits to the plasma NMP data for rat oral exposures were of a similar quality to that shown in Figure 5 of Poet et al. (2010), first figure below.

Fits to the corresponding data for urinary clearance of 5HNMP in the second plot below (not shown by Poet et al., 2010) are also considered adequate, given that the metabolite is not considered to be the proximate toxicant. That the NMP plasma levels (middle curve in first plot) observed by Ghantous (1995) for a dose of 57 mg/kg are roughly 50% of those observed by Midgley et al. (1992) for a 112 mg/kg exposure while the 5HNMP levels observed by Ghantous (1995) were 80% of those reported by Midgley et al. (1992) suggests either an experimental discrepancy or a nonlinearity in 5HNMP clearance that is not well captured by the model. It should be noted that the model does describe well the urinary clearance of 5HNMP after a range of IV and inhalation exposures, as validated in the following QA report. Since the U.S. EPA is not using 5HNMP levels as an internal dose metric, this particular discrepancy in the oral data is not considered severe enough to preclude the PBPK model for use.

Revised PBPK Model Simulations vs. Data for Oral Gavage Exposures of NMP to Rats



Additional references (not included in following contractor's report)

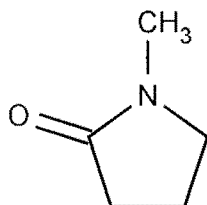
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**A PK/PBPK MODEL QUALITY ASSURANCE ASSESSMENT FOR THE TSCA
WORKPLAN RISK ASSESSMENT OF *N*-Methylpyrrolidone**

(CAS RN 872-50-4)



**Under Battelle Prime Contract EP-C-09-006:
Physiologically-Based Pharmacokinetic (PBPK) Modeling Technical Support
Work Assignment WA 4-01**

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1 QUALITY ASSURANCE ASSESSMENT

A quality assurance (QA) assessment was conducted for a modified physiologically based pharmacokinetic (PBPK) model for orally ingested, inhaled, or dermally absorbed *n*-methylpyrrolidone (NMP) in rats and humans reported by Poet et al. (2010). The evaluation was conducted to insure that the model structure and parameter values presented by Poet et al. (2010) are accurately reflected in the computer code implementation. Changes to the model code that would more accurately represent the physiology/biology of NMP pharmacokinetics were discussed and implemented. Simulations of rat and human exposures that were presented by Poet (2013) were performed and shown here to demonstrate the ability of the current model code to replicate experimental observations.

2 QA OF NMP MODEL (POET ET AL. 2010)

The initial PBPK model computer code relied upon for the QA assessment was supplied by Battelle/Pacific Northwest National Laboratories. The model code was written in the ACSL programming language and was modified/assessed using the acslXtreme software package (version 3.02.1, Aegis Technologies, Inc.). Separate code files were provided for the rat and human models.

2.1 QA of NMP Model Parameters

The NMP model parameter values in the provided model code were checked against the values published in Poet et al. (2010), as well as with Brown et al. (1997) for physiological values and Gentry et al. (2002) for pregnancy-related growth rates. Rat and human model parameter values were assigned in acsl command files (m files), which set parameter values (including exposure conditions), invoke simulation runs, and plot the resulting simulations. Several rat model parameter values included in the acsl model code were different from the values provided in Tables 1, 2, and 5 of Poet et al. (2010). Differences in rat model parameters included the molecular weight for the modeled metabolite, 5-hydroxy-N-methyl-2-pyrrolidone (5-HNMP), fractional blood flow to the mammary glands, uterus, and skin, lung tissue volume, first order urinary elimination rate of 5-HNMP, and equilibrium tissue:blood partition coefficients for NMP in the lung and slowly-perfused lumped tissues compartments (Table 1). The reference for the rat tissue:blood partition coefficients for NMP used in the model code for the placenta (0.309) and for 5-HNMP for placenta and rest-of-body (1.07 and 0.73, respectively) were not provided in the model code or cannot be estimated based on the information provided in Table 5 of the Poet et al. (2010) paper.

Similarly, the human model command files assigned parameter values that were different from published values for molecular weight for NMP, fractional blood flow to the skin and uterus, NMP vapor permeability constant, and fat:blood partition coefficient for 5-HNMP (Table 1). Additionally, source references for tissue:blood partition coefficient values for NMP in the placenta and rapidly-perfused tissues (0.31 and 0.94) and 5-HNMP in the rapidly- and slowly-perfused tissues and rest-of-body (6.5 and 1.0) were not provided in the model code or cannot be determined based on the information provided in Table 5 of Poet et al. (2010) paper.

2.2 QA and Modification of NMP Model Equations

The equations used in the model code to calculate rates of change, amounts, concentrations, and area-under-the-curve (concentration x time) of NMP and 5-HNMP absorption, distribution, metabolism, and elimination in blood and tissues were examined to assure that they accurately represented the model structure and relationships described by Poet et al. (2010). Poet et al. (2010) implemented equations for pregnancy-related changes in body weight, tissues volumes, pulmonary ventilation, and cardiac output used by Gentry et al. (2002). The only differences identified in the pregnancy-related growth equations were for the fetal compartment in rats. Gentry et al. (2002) described fetal growth as having three different phases beginning on the gestation days 0, 11, and 18, whereas the provided NMP model code implemented these changes in fetal growth rates on gestation days 0, 10, and 17. It was not clear if these differences in modeled fetal growth phases may be due to differences between the Poet et al. (2010) and Gentry et al. (2002) in defining time for onset of gestation in rats.

Two modifications were made by EPA staff to the code prior to the QA assessment and included:

- a) Changing the body weight scaling exponent from 0.74 to 0.75 for all allometrically-scaled parameters, and
- b) Correcting the rate equation for dermal absorption of liquid NMP (RADL and RASL for rat and human models, respectively) of NMP from

$$\text{RADL} = ((\text{KPL} \times \text{SA} / 1000) \times \text{CSURF}) - (\text{CSK}/\text{PSK})$$

to

$$\text{RADL} = (\text{KPL} \times \text{SA} / 1000) \times (\text{CSURF} - (\text{CSK}/\text{PSK}))$$

in the rat model, and from

$$\text{RASL} = ((\text{PVL} \times \text{SA}/1000) \times \text{CSURF}) - (\text{CVSK}/\text{PSKL})$$

to

$$\text{RASL} = (\text{PVL} \times \text{SA}/1000) \times (\text{CSURF} - (\text{CVSK}/\text{PSKL}))$$

in the human model.

In addition, several errors in parameters for skin volumes (total body skin or exposed skin only) and equations calculating tissue-specific NMP concentrations in the human model were identified by the EPA WAM, Paul Schlosser, and were corrected. The corrections include selection of an exposure-specific skin volume to use in calculating NMP vapor absorption, introducing a term in the vapor absorption rate that accounts for evaporative NMP loss from the skin (after exposure cessation), corrections in calculating NMP concentration leaving the skin and entering the venous circulation, correction in the calculation of cardiac output and tissue volume of the slowly-perfused compartment by removing the skin volume term, and introduction of spray-on NMP dermal exposures. Also, the human model code was modified to remove discontinuities in placental blood flow at time zero (causing the model to crash) and fat, mammary, and uterine volumes. Pregnancy-related cardiac output and volume growth changes for 5-HNMP in fat were not properly reflected in the slowly-perfused compartment. This resulted in a blood flow mismatch and an artificial loss of 5-HNMP. A detailed description of all of these changes is provided in Appendix B.

In the human NMP model, the parameter for rate of daily NMP ingestion in drinking water (DRINK, mg/kg/day) is included in the equation for rate of NMP change in the liver (RALiv), but should more appropriately be placed in the equation for rate of NMP change in the stomach (RSTOM). As a practical matter, the differences in NMP dose metrics from average daily drinking water doses being introduced in the liver compartment versus the stomach are likely to be negligible.

3 NMP MODEL OUTPUT

Select simulations in rats and humans were run using the code with modification as outlined in Section 2 (referred to hereafter as the modified EPA model). The resulting output was compared with output from the same simulations presented in the Poet (2013) report, which presented a metabolism-re-optimized version of the model code relied upon in Poet et al. (2010), as well as experimental observations, where available. Figure 1 shows the comparative simulations of the Poet (2013) model, the modified EPA

model to the concentrations of NMP measured in blood following a single IV injection of 0.1 (Payan et al. 2002) or 45 mg/kg (Wells and Digenis 1988). Figure 2 provides model estimates of 5-HNMP concentrations in blood and urine, as well as the corresponding measured concentrations, following single IV injections of 0.1 – 500 mg/kg NMP (Payan et al. 2002). In both Figures, minimal differences were seen between the Poet (2013) and modified EPA models in predicting blood or urine levels of NMP and 5-HNMP.

Figure 3 shows measured and model estimated concentrations from both the Poet (2013) and modified EPA models of plasma NMP in rats following a single dermal application of 200 μ L neat NMP (Payan et al. 2003). The Poet (2013) and modified EPA models replicated the experimental observations equally well, with slight over- and under-predictions of the plasma profiles, respectively. Thus, the modified EPA NMP model code is capable of reproducing plasma and urine profiles of NMP and 5-HNMP in rats.

The Poet (2013) and modified EPA models for NMP in humans were used to simulate acute inhalation and dermal exposures. Figures 4 and 5 provide the measured and model estimated concentrations (for both the Poet and modified EPA models) of NMP or 5-HNMP in blood or urine of volunteers inhaling 10–80 mg NMP/m³ for six hours (Poet et al. 2010). Model-predicted NMP levels in plasma and 5-HNMP levels in plasma and urine using the modified EPA code were slightly closer to experimental observations at 39 and 80 mg/m³ than were predictions using the Poet (2013) code. However, the Poet (2013) code predicted NMP in urine levels that were closer to experimental observations than predicted by the modified EPA model. The output from both model codes (Figure 6) produce very similar simulations of plasma NMP in human volunteers inhaling 10 – 53 mg/m³ NMP (Akesson and Paulsson 1997).

For human dermal exposure simulations (Figures 7 and 8), the estimated plasma 5-HNMP concentrations from the modified EPA model code replicated the profiles of the experimental observations (Akesson et al. 2004), which was not the case for urinary 5-HNMP, in which model predictions using the modified EPA model for both males and females were approximately 25-30% lower than experimental observations (Figure 7). The lower model predictability of the urinary data may be due to lower urine production in the volunteers, compared to the assumed 2 L/day production used in the model. Lower urine volume in the experimental subjects could result in higher 5-HNMP levels, compared to model predictions. Finally, the dermal simulations of the Akesson et al. (2004) experiments using modified EPA code (Figure 9) comport with statements by Akesson et al. (2004) that 6-hour dermal exposures to neat NMP would likely result in similar plasma NMP levels to those seen previously following 10 mg/m³ inhalation exposures (Akesson and Paulsson 1997).

4 CONCLUSIONS

The NMP PBPK model code of Poet et al. (2010), as re-optimized by Poet (2013), for rats and humans, was modified by EPA and provided to ENVIRON for use in a QA assessment of the model for use in risk assessment. The modified EPA model code and the Poet (2013) models generally produced very similar simulations following IV and dermal exposures in rats and inhalation and dermal exposures in humans. The modified EPA model provides predictions of plasma NMP levels in both species that were closer to experimental observations than were urinary metabolite predictions. Thus, the modified EPA model code is capable of predicting parent compound and metabolite profiles from multiple data sets providing blood and urine measurements in rodents and humans exposed to NMP by multiple routes of exposure (IV, dermal and inhalation).

5 REFERENCES

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Table 1. Differences between NMP PBPK model parameter values found in the provided model computer code and Poet et al. (2010)

Species	Parameter	Parameter name	Value provided in model computer code	Value published by Poet et al. (2010)
Rat	Molecular weight for 5-HNMP	MWHP	116.14	115.13
Rat	Percent cardiac output to skin	QSKNC	5.8	1.0
Rat	Percent cardiac output to mammary gland	QMAMC	0.1	0.2
Rat	Percent cardiac output to uterus	QUTRC	0.1	0.5
Rat	First-order urinary elimination rate of NMP (L/hr)	KLC	3.9	4.9
Rat	Slowly-perfused tissue:blood NMP partition coefficient	PS	0.74	0.57
Rat	Lung tissue:blood NMP partition coefficient	PLU	0.10	0.13
Human	Molecular weight for 5-HNMP (g/mol)	MWHP	116.14	115.13
Human	Percent cardiac output to skin	QSKNC	5.8	3.0
Human	Percent cardiac output to uterus	QUTRC	0.5	0.62
Human	NMP vapor permeability coefficient (cm/hr)	PV	32	23

Figure 1. Reproduction of Wells and Digenis (1988) and Payan et al. (2002) IV NMP exposures: Plasma profiles

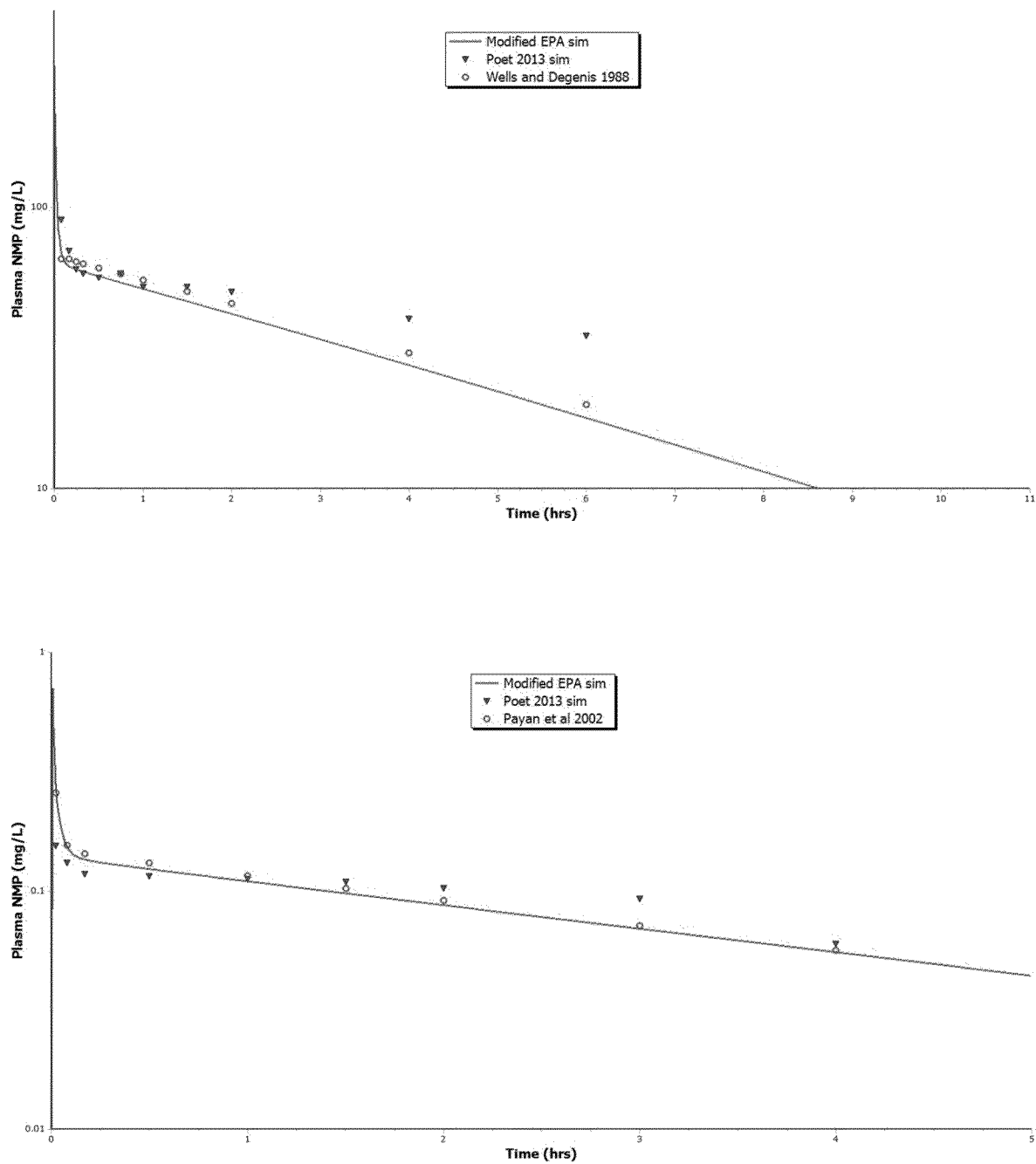


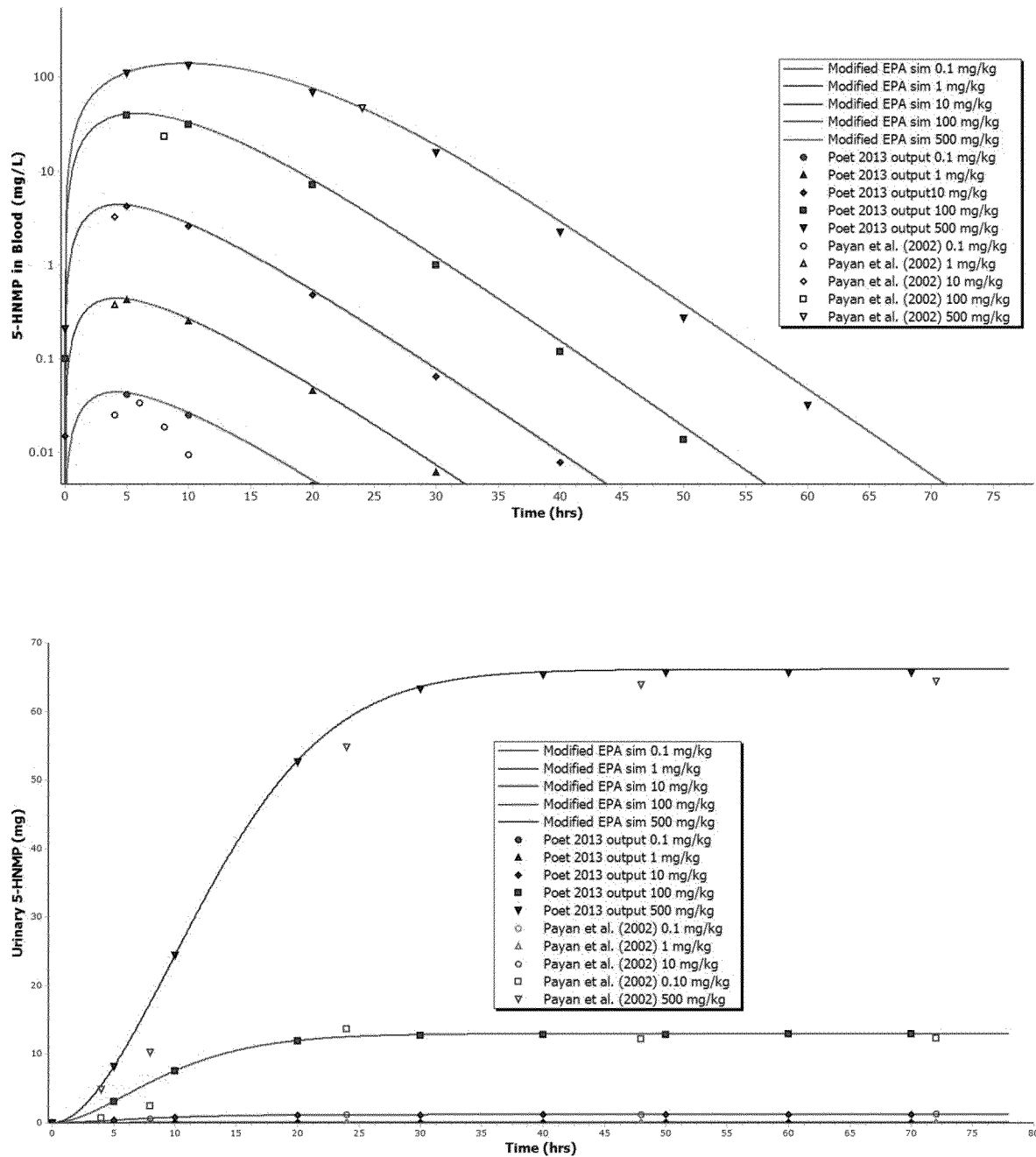
Figure 2. Reproduction of Payan et al. (2002) IV NMP exposures

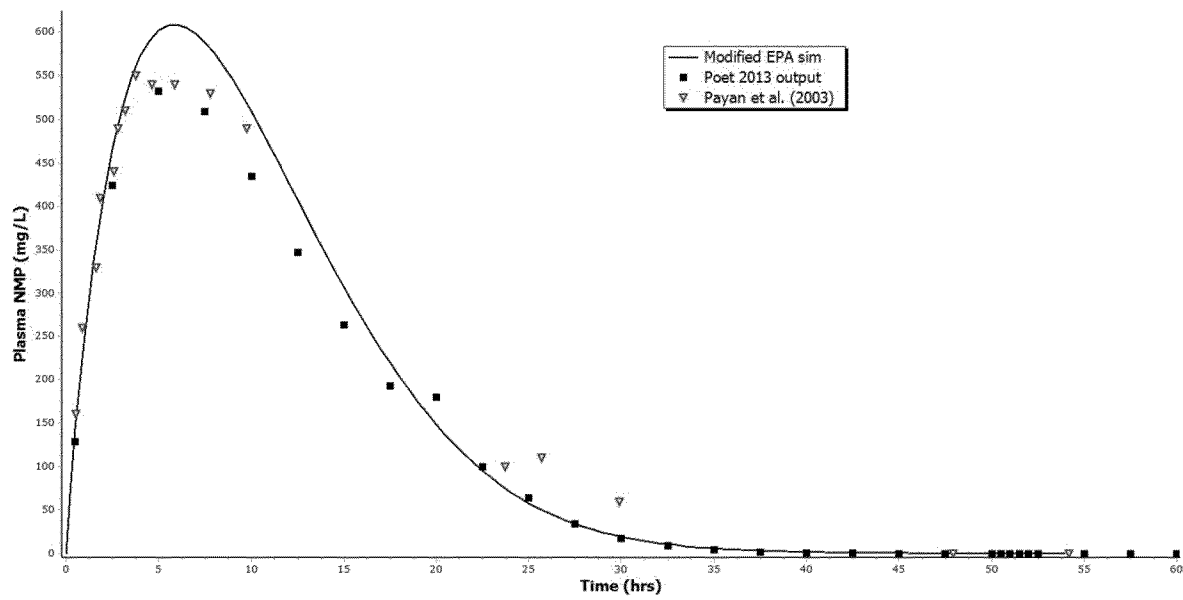
Figure 3. Reproduction of Payan et al. (2003) dermal NMP exposure

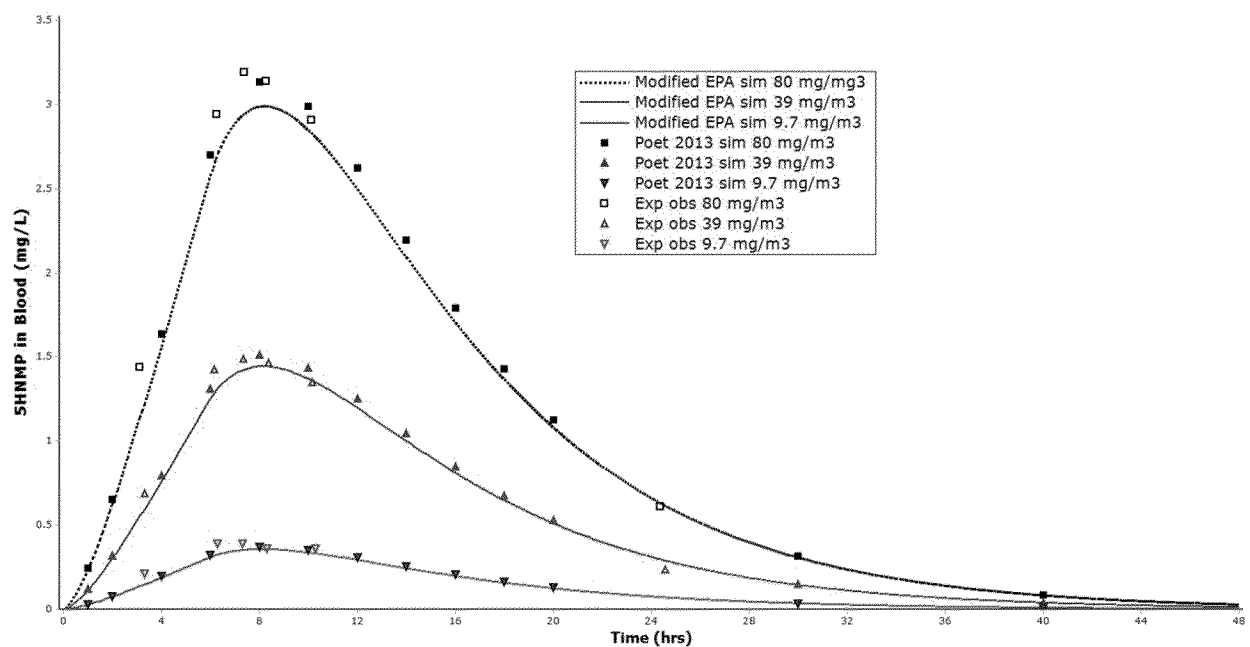
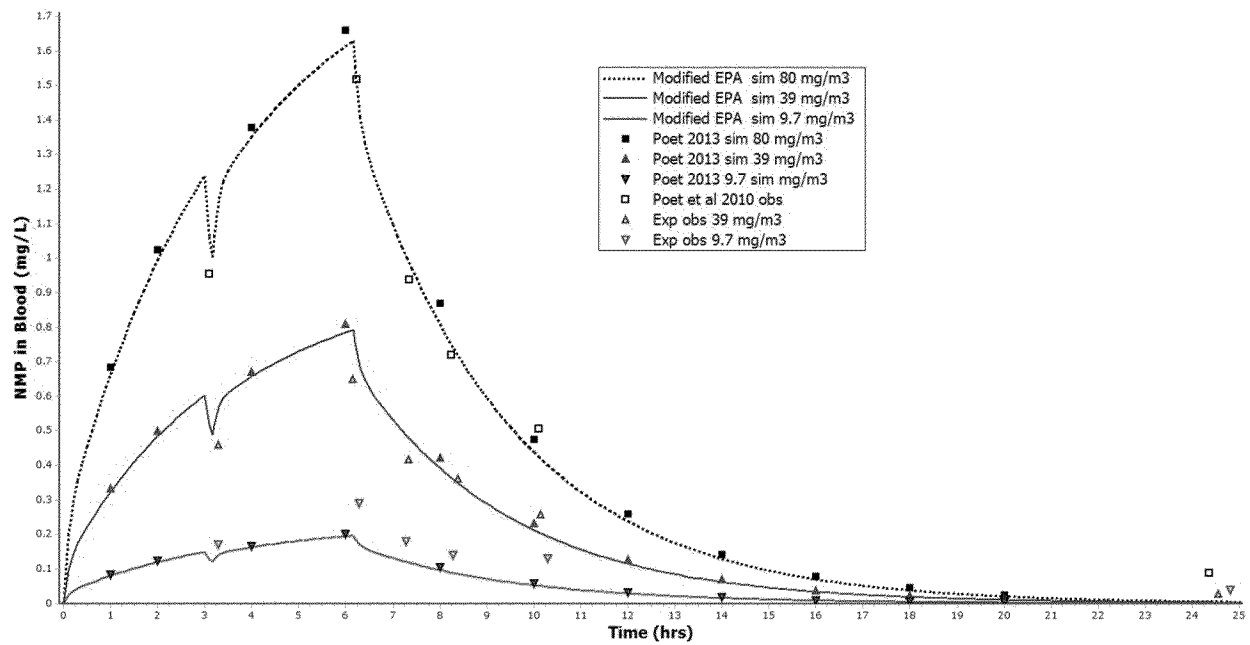
Figure 4. Reproduction of Poet et al. (2010) inhalation NMP exposures: Blood profiles

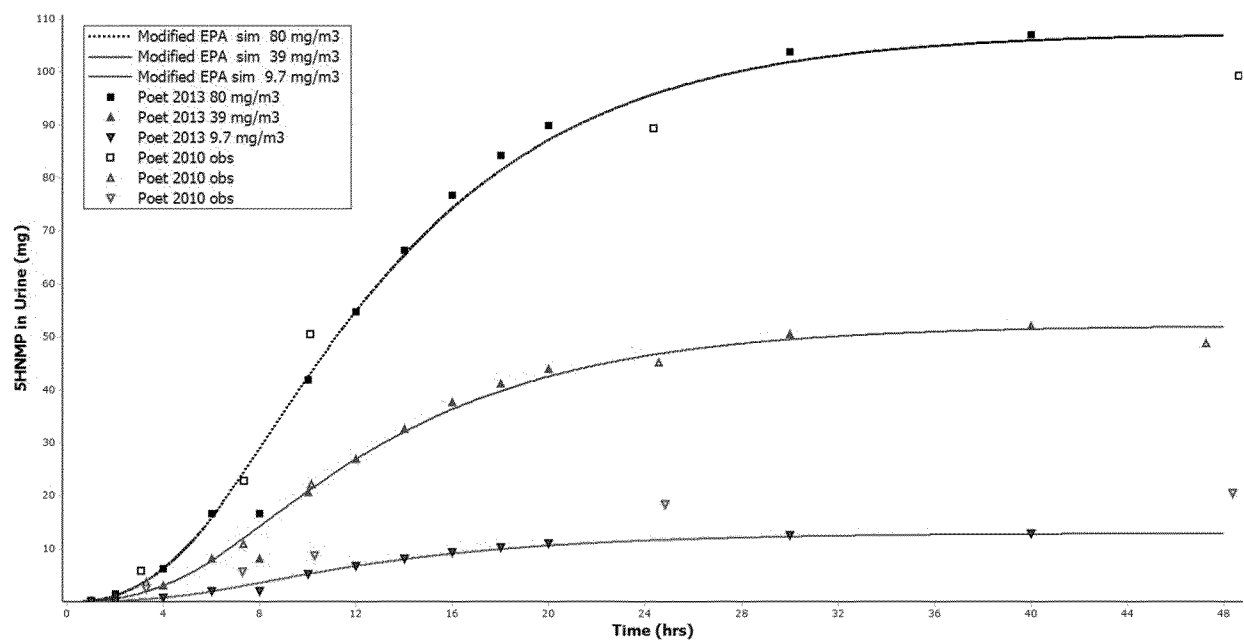
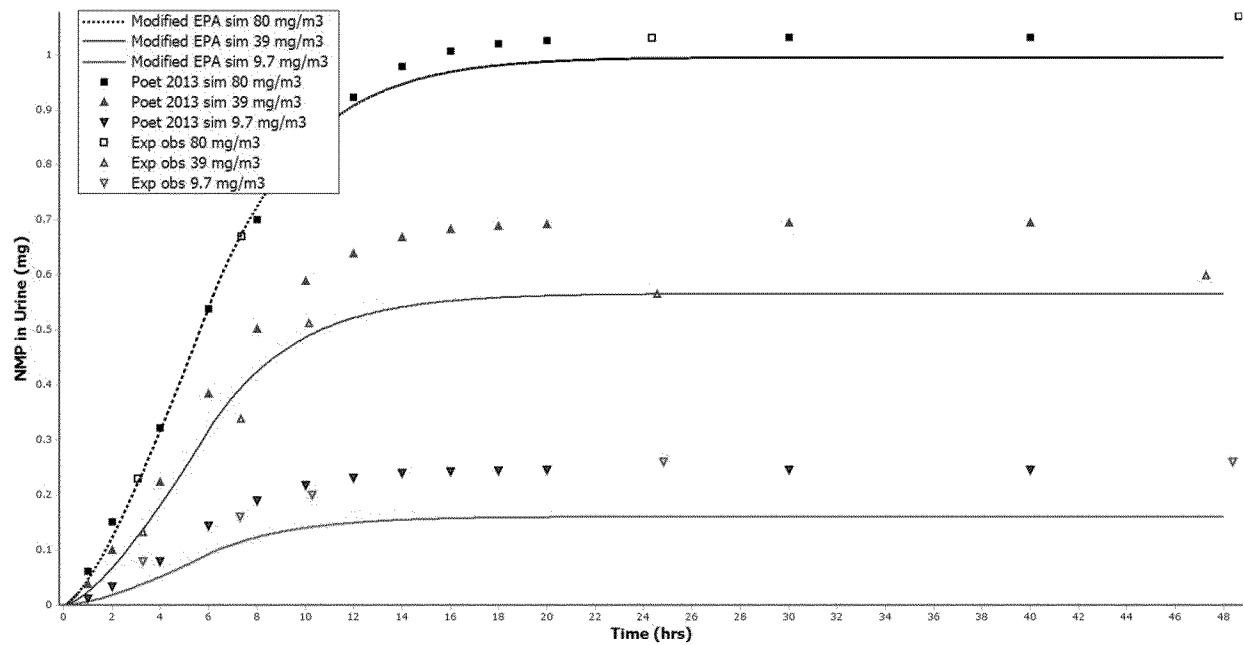
Figure 5. Reproduction of Poet et al. (2010) inhalation NMP exposures: Urine profiles

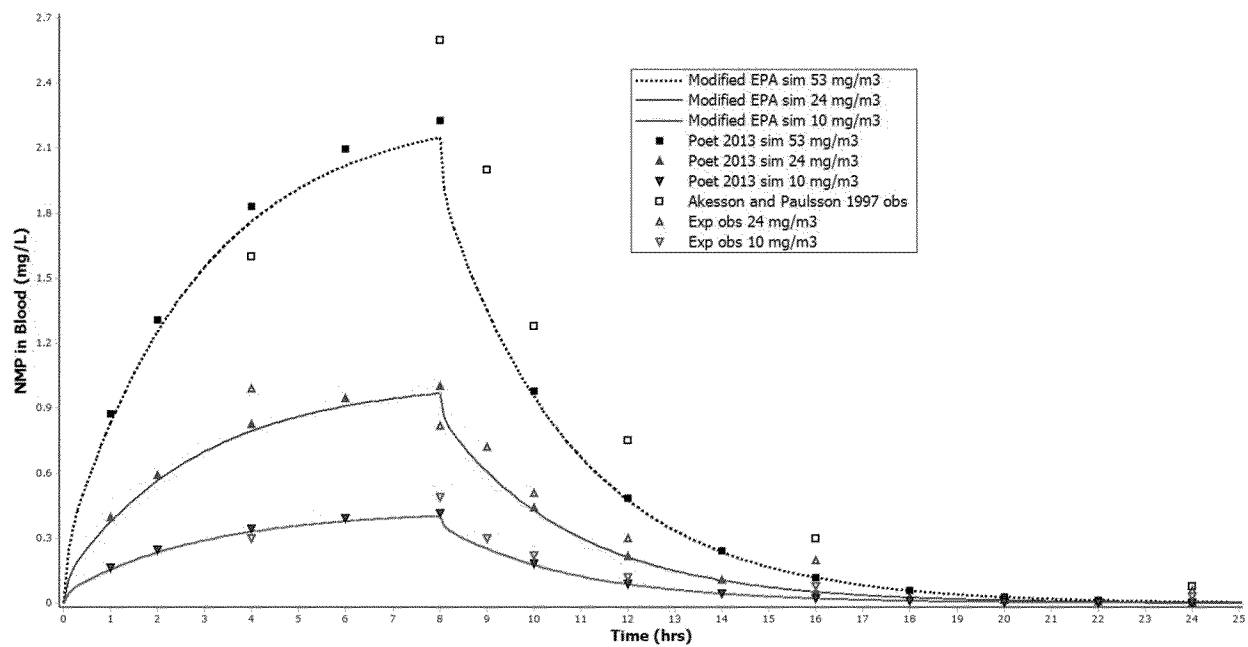
Figure 6. Reproduction of Akesson and Paulsson (1997) inhalation NMP exposures

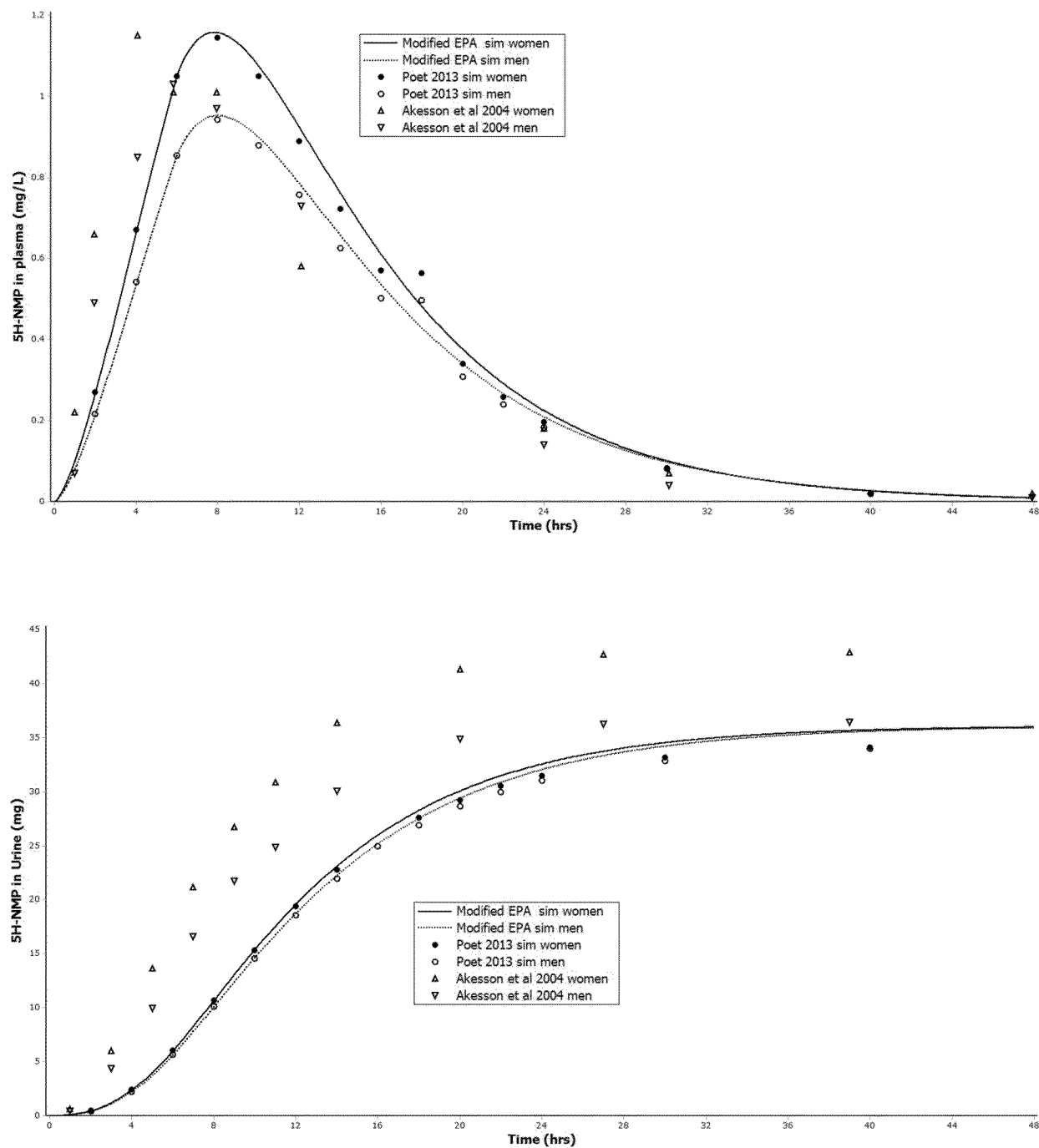
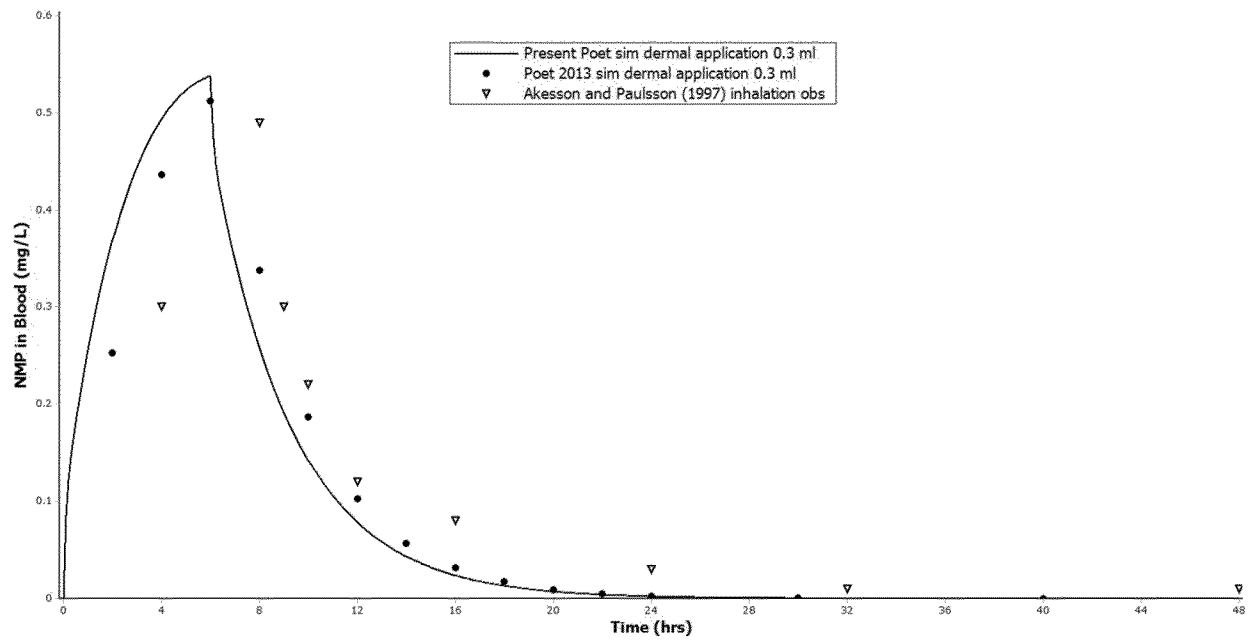
Figure 7. Reproduction of Akesson et al. (2004) dermal NMP exposures

Figure 8. Comparison of Akesson and Paulsson (1997) dermal with inhalation NMP exposures



APPENDIX A. Modified AcslXtreme CSL and M Files Used for the QA Assessment**NMPPREG_RAT.CSL**

PROGRAM NMP.ACSL

!PBPK MODEL FOR N-METHYL PYRROLIDONE

!FINAL RAT MODEL (5/09)

!T.S. POET,P HINDERLITER. CHEMICAL DOSIMETRY GROUP, PNNL, RICHLAND, WA

!MODEL TRANSFERRED FROM SIMUSOLV TO ACSLXTREME FORMAT IN 08

!MODEL CONFIGURED FOR INHALATION (OPEN, WHOLE BODY/NOSE ONLY)

! IV, ORAL, DERMAL, AND IP ROUTES OF ADMINISTRATION.

!MODEL TRACKS DISPOSITION OF NMP AND 5-HNMP.

!ASSUMPTIONS:

! (1) FLOW-LIMITED (ALL COMPARTMENTS)

! (2) METABOLISM OF NMP BY A SAT PATHWAY TO FORM 5HNP

! (3) METABOLISM OF HNP BY SATURABLE PATHWAY TO ETC.

! (5) METABOLISM OCCURS ONLY IN THE LIVER

! (6) TISSUE:BLOOD PART. COEFF. = HUMAN = KRISHNAN EQN

! UPDATED IN CMD FILE TO MEASURED IN-HOUSE

! (7) 5HNP ELIMIN FROM MIXED VENOUS - 1ST ORDER

! THIS DIFFERS FROM 02: URINE BY *GFR CLEARANCE FROM KIDNEY

! METAB RATE CONST. FROM REPORT - UPDATED WITH LIT VALUES IN CMD FILE

! PREG ADDED - OTHER PARAMETERS CHANGED NOMINALLY TO HARMONIZE WITH FETAL IPA MODEL OF

! GENTRY ET AL. REGU TOX PHARM 36:51-68, 2002

INITIAL

! MODEL UNITS

! CONCENTRATION, MG/L

! FLOW, L/HR

! BODY WT, KG

CONSTANT BWINIT=0. ! PRE-PREGNANCY BODY WEIGHT (KG)

CONSTANT RATS=1. !NUMBER OF ANIMALS IN EXPT. NOT USED IN HUMAN MODEL

CONSTANT MWNMP=99.13 !MOL. WT. NMP, MG/MMOL

CONSTANT MWHP= 116.14 !MOL. WT. 5-HNP, MG/MMOL

!BLOOD FLOWS

!FROM BROWN ET AL TOX IND HEALTH 97

!AND/OR FROM IPA MODEL OF GENTRY ET AL.,

! BLOOD FLOWS (FRACTION OF CARDIAC OUTPUT)

CONSTANT QCC = 0 ! CARDIAC OUTPUT (L/HR FOR 1 KG ANIMAL)

CONSTANT QPC = 0 ! ALVEOLAR VENT. RATE

CONSTANT QFATC = 0 ! FAT (NON-PREGNANT)

```

CONSTANT QLIVC = 0      ! LIVER
CONSTANT QMAMC = 0      ! MAMMARY TISSUE (NON-PREGNANT)
CONSTANT QSKNC = 0      ! SKIN
CONSTANT QUTRC = 0      ! UTERUS (NON-PREGNANT)
CONSTANT QRAPC = 0      ! RAPID USE STATIC RAPID FOR RATS (MUST BE CHANGED FOR HUMAN)

```

! PERMEABILITY-AREA PRODUCT (L/HR)

```
CONSTANT PAFC = 0.1      ! DIFFUSION ON FETAL SIDE OF PLACENTA
```

! NOTE 0.1 IS THE VALUE SUPPLIED BY ENVIRON AND USED FOR IPA, IT IS UNSURE WHERE THE VALUE COMES FROM

! GRAPHING OUT TRANSPORT TO FETUS, 0.1 RESULTS IN A MAX FOR NMP, MAYBE FOR IPA AS WELL

! TISSUE VOLUMES (FRACTION OF BODY WEIGHT)

!FROM BROWN ET AL TOX IND HEALTH 97 FOR RATS

!OR FROM GENTRY ET AL

```

CONSTANT VLUC = 0      ! LUNG
CONSTANT VFATC = 0      ! FAT (NON-PREGNANT)
CONSTANT VLIVC = 0      ! LIVER
CONSTANT VMAMC = 0      ! MAMMARY TISSUE (NON-PREGNANT)
CONSTANT VRAPC = 0      ! RAPIDLY PERFUSED
CONSTANT VUTRC = 0      ! UTERUS (NON-PREGNANT)
CONSTANT VBLC = 0      ! TOTAL BLOOD

```

! FOR PARENT MODEL, SKIN COMPARTMENT IS ONLY DEFINED AS DOSED SKIN

```
CONSTANT VSKC = 0.19      ! SKIN
```

```
CONSTANT SA = 0.01      !SURFACE AREA EXPOSED, SQ.CM
```

```
TSA = 906.*BWINIT**(2./3.) !TOTAL BODY SURFACE AREA, SQ.CM.
```

```
!MCDUGAL ET AL. T.A.P. 85(1996)286
```

IF (CONCL.GT.0.0) THEN

```
VSKCC = VSKC*SA/TSA
```

```
QSKCC = QSKNC*SA/TSA
```

ELSE

```
VSKCC = VSKC*SA/TSA
```

```
QSKCC = QSKNC*SA/TSA
```

ENDIF

! SLOWLY PERFUSED (DEFINED AS BALANCE OF TISSUES AND FLOWS)

```
VSC = 0.91 - (VLUC + VFATC + VLIVC + VMAMC + VRAPC + VUTRC + VBLC + VSKCC)
```

! NOTE: 0.91 IS APPROX WHOLE BODY LESS BONE

```
QSC = 1. - (QFATC + QLIVC + QMAMC + QRAPC + QUTRC + QSKCC)
```

! SCALED BLOOD FLOWS (L/HR)

```
QCINIT = QCC * (BWINIT**0.75)      ! CHANGED 0.74 TO 0.75; PMS 8-19-13
```

```
QFATI = QFATC * QCINIT
```

```
QLIV = QLIVC * QCINIT
```

```
QMAMI = QMAMC * QCINIT
```

```
QRAP = QRAPC * QCINIT
```

```
QSKN = QSKCC * QCINIT
```

QSLW = QSC * QCINIT
 QUTRI = QUTRC * QCINIT

! SCALED TISSUE VOLUMES (L)

VLU = VLUC * BWINIT
 VFATI = VFATC * BWINIT
 VLIVI = VLIVC * BWINIT
 VRAP = VRAPC * BWINIT
 VSLW = VSC * BWINIT
 VMAMI = VMAMC * BWINIT
 VUTRI = VUTRC * BWINIT
 VSK = VSKCC * BWINIT
 VBL = VBLC * BWINIT ! TOTAL BLOOD
 VA = 0.25*VBL !ARTERIAL BLOOD
 VV = 0.75*VBL !VENOUS BLOOD

! PREGNANCY PARAMETERS

CONSTANT NUMFET = 7.0 ! NUMBER OF FETUSES (NOT USED FOR HUMAN, ASSUME 1)
 CONSTANT PUPBW = 4500. ! BIRTH WEIGHT (MG)
 CONSTANT VFETD18 = 1051.254 ! VOLUME OF FETUS AT DAY 18 () OF PREGNANCY

! CONVERSION FACTORS

CONSTANT MGKG = 1.0E6 ! CONVERSION FACTOR FROM MG TO KG

!PARTITION COEFFICIENTS

!EXPERIMENTALLY MEASURED VALUES

CONSTANT PB=0. !NMP BLOOD:AIR
 CONSTANT PF=0 !NMP FAT:BLOOD - MEASURED
 CONSTANT PL=0 !MEASURED
 CONSTANT PR=0 !MEASURED LIVER
 CONSTANT PS=0 !NOT MEASURED MUSCLE - CORRECTED FOR FILTER ERROR USING SKIN

PROPORTIONALITY

CONSTANT PSKL=0 !MEASURED
 CONSTANT PLU=0 !NMP LUNG:BLOOD
 CONSTANT PSKA= 0 !NMP SKIN:AIR
 CONSTANT PSKB=0 ! NMP SKIN:BLOOD

! CODE FOR SKIN-AIR TRANSFER IS COMMENTED OUT BELOW, HENCE PSKA IS NOT USED; PAUL SCHLOSSER, U.S. EPA 5-17-13

! CONSTANT PSKL=0 !MEASURED
 CONSTANT PM=0 !MAMMARY, ESTIMATED FORM LIVER
 CONSTANT PPLA=0
 CONSTANT PUTR=0

!EXPERIMENTALLY MEASURED VALUES

CONSTANT PLHNP=0 ! LIVER MEASURED
 CONSTANT PBHNP=0 !ESTIMATED AVG OF "OTHER" TISSUES
 CONSTANT PFHNP=0 !MEASURED

CONSTANT PPLHNP=0

!METABOLIC RATE CONSTANTS

!**THESE ARE FROM PAYAN ET AL

!NMP TO 5HNP

CONSTANT KM=0 !MICHAELIS CONSTANT, MG/L

CONSTANT VMAXC=0 !MAX. ENZ. ACT., MG/HR/L

VMAX1 = VMAXC*BWINIT**0.75

!5HNP TO OTHER METABS

CONSTANT KM2=0 !MICHAELIS CONSTANT, MG/L

CONSTANT VMAX2C=0 !MAX. ENZ. ACT., MG/HR/L

VMAX2 = VMAX2C*BWINIT**0.75

!URINARY ELIMINATION OF 5-HNMP - CLEARED FROM BLOOD

!NOTE FIRST ORDER RATE COMMENTED OUT, SATURABLE FITS BETTER

CONSTANT KLC=0

KL=KLC/(BWINIT**0.25)

CONSTANT KLNC=0 !URINARY LOSS OF NMP, L/HR

KLN=KLNC/(BWINIT**0.25)

!FRACTIONAL ABSORPTION

CONSTANT FRACIN = 1 !FRACTIONAL UPTAKE OF NMP BY INHAL, START AT 65%
!OF ALVEOLAR - AS IN AKESSON ET AL 1997

CONSTANT FRACOR = 1.0 !FRACTION ABSORBED ORALLY, INITIALLY 100%

CONSTANT FRACF=1

! INITIAL CONDITIONS FOR CLOSED CHAMBER INHALATION

CONSTANT VCHC = 9E9 ! VOLUME OF CLOSED CHAMBER (L), START LARGE FOR OPEN

CONSTANT KLOSS = 0.0 ! CHAMBER LOSS RATE /HR

!TIMING COMMANDS

CONSTANT TCHNG=6.0 !END OF INHAL EXPOSURE, HR

CONSTANT TSTOP=24.0 !END OF EXPERIMENT/SIMULATION, HR

CONSTANT MAXT=0.01 !MAXIMUM STEP SIZE, HR THIS MAY NEED SET LOWER FOR

NEW VERSION OF ACSL TO RUN

CONSTANT MINT=1E-7

CONSTANT CINT = 0.2 !DATA LOGGING RATE /HR

CONSTANT GDDAYS=0.0 ! OFFSET FOR GESTATIONAL DAY SIMULATION

CONSTANT GDMONTHS=0.0 !OFFSET FOR HUMAN GD SIMULATION

!INITIAL EXPOSURE CONDITIONS

! EXPOSURE CONDITIONS BASED ON USER DEFINED INITIAL AMOUNTS OF CHEMICAL (MG)

CONSTANT CONCPPM = 0.0 !AIR CONCENTRATION IN PPM!

```

        CONSTANT CONCMGS = 0.0
        ! USED TO SET AIR CONC'N AS MG/M3, PMS, 8-13-13
        VCH = VCHC-(RATS*BWINIT)      !VOLUME OF OCCUPIED CHAMBER
        CONCMG = CONCMGS/1000 + CONCPPM*MWNMP/24451.  !CONVERT PPM TO MG/LITER!
        CONSTANT DOSEINTERVAL=24      !TIME BETWEEN DAILY DOSES
        CONSTANT CONCCHPPM0 = 0      ! INITIAL PPM IN CLOSED CHAMBER
        CONCHMG0= CONCCHPPM0*MWNMP/24451.
        ACHO = CONCHMG0 * VCH      !INIT. AMT IN CHAMBER, MG!
!ORAL
        CONSTANT KAS=1.0      !1ST ORDER RATE CONST FOR ORAL ABS,HR-1
        CONSTANT DOSE=0.0      !ORAL DOSE IN MG/KG BW
        ODOSE = DOSE*BWINIT      !CONVERT MG/KG BW TO MG TOTAL(ORAL)
        !**NOTE - CONSIDER ADDING ZERO ORDER FOR HUMAN HED
        CONSTANT DOSE2=0.0      ! ORAL DOSE IN MG/KG
        BW, BUT TOTAL DOSE INCREASES W/ BW

!FEED
        CONSTANT KASF=1.0      !1ST ORDER RATE CONST FOR ORAL ABS,HR-1
        CONSTANT DOSEF=0.0      !ORAL DOSE IN MG/KG BW
        ! TABLE FEEDDOSE 1 ,10 /10*24.,10*1./
!IV
        CONSTANT IVDOSE=0.0      !IV DOSE, MG/KG NMP
        CONSTANT TINF=0.01      !DURATION OF IV INFUSION, HR, SET TCHNG=TINF
!DERMAL
        CONSTANT CONCL = 0.0      !CONC OF NMP IN LIQUID, MG/L
        CONSTANT KPL = 0.0      !PERM COEFF FOR LIQUID, CM/HR
        CONSTANT VLIQ = 1.0E-99      !INITIAL VOLUME APPLIED, L
        CONSTANT DENSITY=      1.03
        CONSTANT DSK=0.0      ! INITIAL AMOUNT (MG/KG BW) RUBBED INTO SKIN;
PMS 8-14-13
        ASKO=DSK*BWINIT      ! PMS, 8-14-13
        CONSTANT TWASH=8.0      ! WASH TIME IN BECCI ET AL. (1982) EXPOSURES
        !CONSTANT RESID=0      !AMOUNT STICKING TO EXPOSURE SYSTEM, MG
        ! DDN = CONCL*VLIQ
        CONSTANT FAD=0.222      !FRAC NO ABSORBED IN PAYAN ET AL
        !IN VITRO HUMAN VAN DYK ET AL. AIHA J 56: 651-660
        !START WITH SMALL SA SO VSKE IS NON-ZERO (USED IN DENOMINATOR OF CSK CALCULATION)

!IP
        CONSTANT IPDOSE = 0.0      !IP DOSE, MG/KG NMP
        CONSTANT KIP=1.0      !1ST ORDER RATE OF ABS, HR-1
        PDOSE = IPDOSE*BWINIT      !TOTAL IP DOSE, MG

!DOSING SCHEDULE
        IF (DSK.GT.0.0) THEN
                SCHEDULE SKWASH.AT.TWASH
        ENDIF
        SCHEDULE OFFD.AT.TCHNG      !TURN OFF EXPOSURE AT TCHNG
        CIZONE = 1.0      !START WITH INHALATION ON

```

```

IVZONE = 1.0      !START WITH IV ON
IF (CONCL.GT.0.0) THEN
  DZONE = 1.0      !START WITH DERMAL ON
ELSE
  DZONE = 0.0
ENDIF
CONSTANT TSTART=0.2 ! OFFSET START-TIME FOR GAVAGE DOSING
      SCHEDULE GAVD.AT.TSTART
      ALGORITHM IALG=2      !GEAR ALGORITHM

END

DYNAMIC

DERIVATIVE
!=====FETAL AND BW CHANGES W/PREGNANCY=====
      GDMONTH=GDMONTHS/0.64!TO WAG HUMAN GROWTH, THIS SETS HUMAN FETAL
                                   !AT BIRTH ~3.5 KG AND MOTHER GAINING ~ 8.7
KG                                   !ACTUAL HUMAN AT BIRTH AVERAGE IS 3.5 KG
                                   !MOTHER AT BIRTH GAINS 13.6 KG

      HOURS = T
      MINUTES = T * 60.0
      DAYS = T / 24.0 + GDDAYS +GDMONTH

! VOLUME OF FAT (L)
      VFAT = VFATI * (1.0 + (0.0165 * DAYS))

! VOLUME OF FETUS (KG)
! ADDED 1.0E-8 TO VARIOUS VOLUMES TO AVOID DIVIDE-BY-ZERO PROBLEMS; PMS 8-13-13
      IF (DAYS.LT.10.0) THEN
        VFET = (1.0E-8 + NUMFET * ((0.1206 * DAYS)**4.53)) / MGKG
      ELSE IF (DAYS.LT.17.0) THEN
        VFET = (1.0E-8 + NUMFET * ((1.5 * (DAYS - 9))**2.8)) / MGKG
      ELSE
        VFET = (1.0E-8 + NUMFET * (VFETD18 + (((PUPBW - VFETD18) / 4.0) * (DAYS - 17)))) / MGKG
      ENDIF

! VOLUME OF MAMMARY TISSUE (L)
      VMAM = VMAMI * (1.0 + (0.27 * DAYS))

! VOLUME OF PLACENTA (L)
      IF (DAYS.LT.6.0) THEN
        VPLA = 1.0E-8
      ELSE IF (DAYS.LT.10.0) THEN
        VPLA = (1.0E-8 + NUMFET * (8. * (DAYS - 6.))) / MGKG
      ELSE

```

```

      VPLA = (1.0E-8 + NUMFET * ((32 * EXP(-0.23 * (DAYS - 10))) + (40 * (EXP(0.28 * (DAYS - 10)) - 1)))) /
MGKG
      ENDIF

```

```

! VOLUME OF UTERUS (L)
  IF (DAYS.LE.3.0) THEN
    VUTR = VUTRI
  ELSE
    VUTR = VUTRI * (1.0 + (0.077 * ((DAYS - 3.)**1.6)))
  ENDIF

```

```

!VOLUME OF LIVER INCREASE !CORLEY ET AL CRC 03,BUELKE-SAM ET AL '82 AND OTHERS
  IF (DAYS.LT.5.0) THEN
    VLIV=VLIVI
  ELSE
    VLIV= VLIVI * (1.0 + (0.0455 * ((DAYS - 5.0))))
  ENDIF

```

```

! INCREASE IN BODY WEIGHT (KG)
  ! WATER=(0.0033*DAYS)+(9.2E-5*(DAYS**2)) !CORLEY ET AL CRC 03,
    BW = BWINIT + (VFAT - VFATI) + VFET + (VMAM - VMAMI) + VPLA + (VUTR -
VUTRI)+(VLIV - VLIVI)

```

```

! SCALED ALVEOLAR VENTILATION (L/HR)
  QP = QPC * ((BW-VFET-VPLA)**0.75)      ! CHANGED 0.74 TO 0.75; PMS 8-19-13

```

```

! INCREASE IN BLOOD FLOWS (L/HR)
  QFAT = QFATI * (VFAT / VFATI)
  QMAM = QMAMI * (VMAM / VMAMI)
  QUTR = QUTRI * (VUTR / VUTRI)
!!!!!! NOTE THAT THE BLOOD FLOWS NO LONGER BALANCE. QP HAS INCREASED BY THE ADDITIONAL
!!!!!! FETAL AND PLACENTAL VOLUMES BUT THE COMPARTMENTAL FLOWS HAVE NOT CHANGED.
!!!!!! QRECOV WILL START AT 100 AND DECREASE THRU PREGNANCY (PMH 25-APR-2007)

```

```

! TOTAL BODY FOR HNMP
  QB = QRAP+QSLW+QSKN+QMAM+QUTR ! +QPLA ! PLACENTA IS A SEPARATE COMPARTMENT;
PMS 8-19-13
  VB = VRAP+VSLW+VLU+VSK+VMAM+VUTR ! +VPLA ! DITTO; PMS 8-19-13

```

```

! BLOOD FLOW TO PLACENTA (L/HR)
  IF (DAYS.LT.6.0) THEN
    QPLA = 0.0
  ELSE IF (DAYS.LT.10.0) THEN
    QPLA = (NUMFET * (0.55 * (DAYS - 6.0))) / 24
  ELSE IF (DAYS.LE.12.0) THEN
    QPLA = (NUMFET * (2.2 * EXP(-0.23 * (DAYS - 10)))) / 24
  ELSE

```

```

      QPLA = (NUMFET * ((2.2 * EXP(-0.23 * (DAYS - 10)))+ ((0.1207 * (DAYS - 12.0))**4.36))) / 24
    ENDIF

```

```

! INCREASED CARDIAC OUTPUT (L/HR)

```

```

      !QC = QCINIT + (QFAT - QFATI) + (QMAM - QMAMI) + QPLA + (QUTR - QUTRI)

```

```

      QC = QFAT+QLIV+QSLW+QRAP+QSKN+QMAM+QPLA+QUTR! PMS, 8-13-13

```

```

! SCALED PERMEABILITY-AREA PRODUCT

```

```

      PAF = PAFC * (VFET**0.75)

```

```

!=====FIRST MODEL FOR TRACKING NMP=====

```

```

!EQUATIONS FOR ORAL GAVAGE DOSING

```

```

      RAO = KAS * AO*FRACOR

```

```

      AO = INTEG(-RAO,ODOSE) !AMT REMAINING TO BE ABS, MG!

```

```

      OABS = INTEG(RAO,0.0)

```

```

           !ODOSE - AO           !AMT ABSORBED ORALLY, MG!

```

```

!EQUATIONS FOR FEED DOSING

```

```

      FDOSE = DOSEF*BW      !CONVERT MG/KG BW TO MG TOTAL(ORAL)

```

```

      RAF = KASF * AF*FRACF

```

```

      AF = FDOSE - INTEG(RAF,0.0) !AMT REMAINING TO BE ABS, MG!

```

```

      FABS = INTEG(RAF,0.0)

```

```

!AL = AMOUNT NMP IN LIVER COMPARTMENT (MG)

```

```

      RAL = QLIV*(CA - CVL)+ RAIP + RAO + RAF - RAML

```

```

      AL = INTEG(RAL, 0.0)

```

```

      CVL = AL/(VLIV*PL)

```

```

      RAML = (VMAX1*CVL)/(KM+CVL)      !SATURABLE METABOLISM, MG/HR

```

```

      AML = INTEG(RAML,0.0)      !AMT NMP METAB BY SATURABLE PATH, MG

```

```

      AML1B = RATS*AML*MWHP/MWNMP !TOT AMT HNP PRODUCED IN LIVER, MG

```

```

!EQUATIONS FOR IP DOSING

```

```

      RAIP = KIP * AIP

```

```

      AIP = INTEG(-RAIP,PDOSE) !AMT REMAINING TO BE ABS, MG!

```

```

      IPABS = INTEG(RAIP,0.0)

```

```

!EQUATIONS FOR IV INFUSION

```

```

      IVR = IVZONE*IVDOSE*BW/TINF !RATE OF INFUSION, MG/HR

```

```

      TIV = INTEG(IVR,0.0)      !TOTAL AMOUNT INJECTED, MG

```

```

! ARTERIAL BLOOD

```

```

      RAAB = (QC * (CVLU - CA))-RAUNP

```

```

      AAB = INTEG(RAAB, 0.0) !AMOUNT, MG

```

```

      CA = AAB / VA      !CONCENTRATION, MG/L

```

```

      AAUCB = INTEG(CA, 0.0) !AUC, HR*MG/L

```

```

      RAUNP = KLN*CA*VV

```

```

           !FIRST ORDER RATE OF LOSS (URINE)

```

AUNP = INTEG(RAUNP,0.0)

! CHAMBER CONCENTRATION (MG/L)

RACH = (RATS * QP * CLEX) - (FRACIN * RATS * QP * CI) - (KLOSS * ACH)

ACH = INTEG(RACH, ACHO)

! THE FOLLOWING CALCULATION YIELDS AN AIR CONCENTRATION EQUAL TO

! THE CLOSED CHAMBER VALUE IF A CLOSED CHAMBER RUN IS IN PLACE AND

! A SPECIFIED CONSTANT AIR CONCENTRATION IF AN OPEN CHAMBER RUN IS IN PLACE

CCH = (ACH / VCH)! * CIZONE) + (CONCMG * (1.0 - CLON))

CCPPM = CCH * 24451 / MWNMP

CLOSS = INTEG(KLOSS * ACH, 0.0)

CI = CCH * PULSE(0., DOSEINTERVAL, TCHNG) + CIZONE * CONCMG ! MG/L ! ADDED CIZONE * CONCMG,
PMS, 8-13-13

! LUNGS

!RALU = (QP * ((FRACIN * CI) - CLEX)) + (QC * (CV - CVLU))

RALU = (QP * ((FRACIN * CI) - CLEX)) + RVV - (QC * CVLU) ! PMS, 8-13-13

ALU = INTEG(RALU, 0.0)

CLU = ALU / VLU !CONCENTRATION, MG/L

CVLU = CLU / PLU !EXITING CONCENTRATION, MG/L

! AMOUNT INHALED

RINH = FRACIN * QP * CCH * CIZONE

AINH = INTEG(RINH, 0.0) ! MG PER

AINHC = AINH * RATS ! MG FOR A GROUP OF RATS

! AMOUNT EXHALED

CLEX = CV / PB ! CONCENTRATION, MG/L

RAEX = QP * CLEX

AEX = INTEG(RAEX, 0.0) ! AMOUNT, MG PER

AEXC = AEX * RATS ! AMOUNT, MG, FOR A GROUP OF RATS

!ASK = AMOUNT NMP IN SKIN TISSUES (MG) AND DERMAL DOSING

RASK = QSKN * (CA - CSKV) + RADL ! NOW MINUS CSKV, NOT CSK; PMS 8-21-13

ASK = INTEG(RASK, ASKO) ! INITIAL VALUE, ASKO, ADDED FOR BECCI ET AL. (1982) EXPOSURES;
PMS 8-14-13

CSK = ASK / VSK !'NMP IN SKIN, MG/L'

CSKV = CSK / PSKB

! NMP IN VENOUS

BLOOD, PMS 8-22-13

CVSK3 = CSK * 1000 / MWNMP !'NMP IN CVSK, MICROMOL/L'

! RADL = (KPL * SA / 1000) * (CONC2 - (CSK / PSKA)) * DZONE !REPLACE CONCL W CONC2 IF LIQUID

ABSORPTION NEEDED

! ADL = INTEG(RADL, 0.0) !'AMT NMP ABSORBED DERMAL, MG'

! DDA = DDN - RESID !'LESS AMT NMP RECOVERED ON PATCH

```

! ADLA = INTEG(-RADL,DDA)
! ADL2 = ADL*1000/MWNNMP    !'AMT ABSORBED, MICROMOLES'
! CONC2=RSW(VLIQABS1.LE.VLIQ,ADLA/(VLIQ-VLIQABS1),0.01)
! VLIQABS1=ADL/1000/DENSITY/1000

CONCL2=CONCL*FAD
CSURF=(CONCL2-(ADL/VLIQ))*DZONE
!RADL=((KPL*SA/1000)*CSURF)-(CSK/PSK) ! INCORRECT FORM; PMS 8-13-13
RADL=(KPL*SA/1000.0)*((CSURF-(CSK/PSK))*DZONE - (1.0-DZONE)*(CSK/PSKA)) ! CORRECT FORM;
PMS 8-13-13
! 2ND TERM, (1.0-DZONE)*(CSK/PSKA), ALLOWS FOR EVAPORATIVE LOSS WHEN DZONE=0; PMS 8-14-13
ADL=INTEG(RADL,0.0)

```

```

! NOTE - NO LOSS TERM. TRY WITHOUT OR ADD LOSS UP-FRONT BY SUBTRACTING
! AMOUNT RECOVERED FOR EACH STUDY WITH AMOUNT (CONC) ORIGINALLY APPLIED
! "LOSS" OR STICKING PROBABLY ESSENTIALLY IMMEDIATE AND NOT KINETIC
! REPORTS OF ~11-24% STICKING TO DRESSING

```

```

! AMOUNT IN FAT (MG)
RAFAT = QFAT * (CA - CVFAT)
AFAT = INTEG(RAFAT, 0.0)
CFAT = AFAT / VFAT
CVFAT = CFAT / PF

! AMOUNT IN FETUSES (MG)
RAFET = PAF * (CPLA - CFET)
AFET = INTEG(RAFET, 0.0)
!IF (DAYS.GT.6.0) CFET = AFET / VFET
CFET = AFET / VFET    ! PMS, 8-13-13
AUCCFET = INTEG(CFET, 0.0)

```

```

! AMOUNT IN UTERUS (MG)
RAUTR = QUTR * (CA - CVUTR)
AUTR = INTEG(RAUTR, 0.0)
CUTR = AUTR / VUTR
CVUTR = CUTR / PUTR

```

```

! AMOUNT IN MAMMARY TISSUE (MG)
RAMAM = QMAM * (CA - CVMAM)
AMAM = INTEG(RAMAM, 0.0)
CMAM = AMAM / VMAM
CVMAM = CMAM / PM

```

```

! AMOUNT IN PLACENTA (MG)
RAPLA = (QPLA * (CA - CVPLA)) + (PAF * (CFET - CPLA))
APLA = INTEG(RAPLA, 0.0)
! IF (DAYS.GT.6.0) CPLA = APLA / VPLA
CPLA = APLA / VPLA ! PMS, 8-13-13

```

CVPLA = CPLA / PPLA

!AS = AMOUNT IN SLOWLY PERFUSED TISSUES (MG)

RAS = QSLW*(CA - CVS)

AS = INTEG(RAS, 0.0)

CVS = AS/(VSLW*PS)

CS = AS/VSLW

!AR = AMOUNT IN RAPIDLY PERFUSED TISSUES (MG)

RAR = QRAP*(CA - CVR)

AR = INTEG(RAR, 0.0)

CVR = AR/(VRAP*PR)

CR = AR/VRAP

!MIXED VENOUS BLOOD

!RV=(QFAT*CVFAT+QLIV*CVL+QSLW*CVS+QRAP*CVR+QSKN*CSK+CVMAM*QMAM+CVPLA*QP
LA+QUTR*CVUTR+IVR)-QC*CV

RVV = QC*CV ! PMS, 8-13-13

RV=(QFAT*CVFAT+QLIV*CVL+QSLW*CVS+QRAP*CVR+QSKN*CSKV+CVMAM*QMAM+CVPLA*QP
LA+QUTR*CVUTR+IVR)-RVV ! PMS, 8-13-13

AV=INTEG(RV,0.0)

CV=AV/VV

AUCBB=INTEG(CV,0.0) !AUC, HR*MG/L

!-----MASS BALANCE NMP -----

BODY = (AFAT+AR+AS+AL+ASK+AV+ALU+AAB+APLA+AMAM+AUTR)

TMASS = RATS*(BODY + AML + AEX+AUNP+AFET)!COMPARE TO

!AINH FOR OC MASS BAL

!OR OABS FOR ORAL MASS BAL

!OR TIV FOR IV MASS BAL

!OR ADL FOR DERMAL LIQUID

MASBAL=TMASS/(AINH+OABS+TIV+ADL+1E-9)

! CHECK BLOOD FLOWS

QTOT = QFAT + QLIV + QRAP + QSKN + QSLW + QUTRI +QMAM+QPLA

QRECOV = 100.0 * (QTOT / QC)

!=====SECOND MODEL FOR TRACKING HNP=====

!ALHP = AMOUNT HNMP IN LIVER COMPARTMENT (MG)

RALHP = QLIV*(CAHP-CVLHP)+ RAML1 - RAMLH

RAML1=RAML*MWHP/MWNMP

AML2B=INTEG(RAML1,0.0)

ALHP = INTEG(RALHP,0.0) !AMT IN MG HNMP, CORRECTED FOR MW

CVLHP = ALHP/(VLIV*PLHNP) !TOTAL HNMP

RAMLH = (VMAX2*CVLHP)/(KM2+CVLHP) !SATURABLE METABOLISM, MG/HR

AMLH = INTEG(RAMLH,0.0) !AMT HNMP METAB BY SATURABLE PATH, MG

RDOSE=RAMLH/(BW**0.75)

```

TDOSE=INTEG(RDOSE,0.0)

!ABHP = AMOUNT HNMP IN TISSUES (MG)
RABHP = QB*(CAHP - CBSHP)
ABHP = INTEG(RABHP,0.0)
CBSHP = ABHP/(VB*PBHNP)

!AFHP = AMOUNT HNMP IN FAT (MG)
RFSHP = QFAT*(CAHP - CVFHP)
AFHP = INTEG(RFSHP,0.0)
CVFHP = AFHP/(VFAT*PFHNP)

!CVHP = MIXED VENOUS BLOOD CONC TOTAL HNMP (MG/L)
CRHP = (QLIV*CVLHP + QB*CBSHP + QFAT*CVFHP + QPLA*CVPLHP)-QC*CVHP-RAUHP
! ** ADDED QPLA*CVPLHP TO ABOVE; PMS 8-19-13
AVHP = INTEG (CRHP,0.0)
CVHP = AVHP/VBL
CAHP = CVHP
CVHP2 = CVHP*1000/MWHP    !VENOUS BLOOD TOT CONC HNMP IN MICROM

AUCVHP = INTEG(CVHP2,0.0)  !AUC HNMP VEN. BLOOD, MICROMOL*HR/L

! AMOUNT IN PLACENTA (MG)
RAPLHP = (QPLA * (CAHP - CVPLHP)) + (PAF * (CFETHP - CPLHP))
APLHP = INTEG(RAPLHP, 0.0)
!IF (DAYS.GT.6.0) CPLHP = APLHP / VPLA
                CPLHP = APLHP / VPLA    ! PMS, 8-13-13
CVPLHP = CPLHP / PPLHNP

! AMOUNT IN FETUSES (MG)
RAFETHP = PAF * (CPLHP - CFETHP)
AFETHP = INTEG(RAFETHP, 0.0)
! IF (DAYS.GT.6.0) CFETHP = AFETHP / VFET
                CFETHP = AFETHP / VFET    ! PMS, 8-13-13
AUCFETHP = INTEG(CFETHP, 0.0)

!RATE OF ELIM IN THE URINE, RAUHP, FROM MIXED BLOOD
RAUHP = KL*CAHP*VA    !FIRST ORDER RATE
AUHP = INTEG(RAUHP,0.0)  !CUMULATIVE AMT HNMP IN URINE (MG), NOT MGEQ

!-----MASS BALANCE-----
!-----MASS BALANCE 5-HNMP SUBMODEL-----
!COMMENT OUT EQUATIONS WHEN NOT USING TO ELIM. UNESSESARY INTEG
BODYHP = (AFHP+ABHP+ALHP+AVHP+AFETHP+APLHP)*RATS    !+AABH
TMASHP = RATS*(AUHP + BODYHP +AMLH)    !COMPARE TO AML1B

! CHECK BLOOD FLOWS 5HNMP COMPARTMENT
QTOTH = QLIV + QFAT + QB+QPLA

```

QRECOVH = 100.0 * (QTOTH / QC)

TERMT(T .GE. TSTOP) !----STATEMENT TO STOP EXECUTION---

END !END OF DERIVATIVE

DISCRETE GAVD

AO = AO + DOSE2*BW

SCHEDULE GAVD .AT. (T+24.0)

END

!EXPOSURE CONTROL

DISCRETE SKWASH ! PMS, 8-14-13

ASK = 0.0 ! ASSUME SKIN WASHING IN BECCI ET AL. (1982) REMOVES ALL NMP FROM SKIN

IF (DAYS.LT.15.0) SCHEDULE REAPPLY.AT.(T+DOSEINTERVAL-TWASH)

END

DISCRETE REAPPLY ! PMS, 8-14-13

IF (ROUND(DAYS).EQ.9.0) ASKO=DSK*BW

IF (ROUND(DAYS).EQ.12.0) ASKO=DSK*BW

IF (ROUND(DAYS).EQ.15.0) ASKO=DSK*BW

ASK = ASK+ASKO

SCHEDULE SKWASH.AT.(T+TWASH)

END

DISCRETE OFFD

IVZONE=0.0 !TURN IV OFF

CIZONE=0.0 !TURN INHAL EXPOSURE OFF

DZONE=0.0 !TURN OFF DERMAL

SCHEDULE OND.AT.(T+DOSEINTERVAL-TCHNG) ! PMS, 8-13-13

END

DISCRETE OND ! PMS, 8-13-13

CIZONE=1.0 !TURN INHAL EXPOSURE ON

SCHEDULE OFFD.AT.(T+TCHNG)

END

END !END OF DYNAMIC

END !END OF PROGRAM

HUMPREGRETRIEVE_RESTORED_1.CSL

PROGRAM NMPHUMPG.ACSL

!PBPK MODEL FOR N-METHYL PYRROLIDONE IN PREGNANT WOMEN

!T.S. POET,P HINDERLITER. CHEMICAL DOSIMETRY GROUP, PNNL, RICHLAND, WA

!FIRST CREATED 8.8.08

!FINAL REPORT FROM INITIAL RAT MODEL DEVELOPMENT SUBMITTED 9.02

!MODEL CONFIGURED FOR INHALATION (OPEN, WHOLE BODY/NOSE ONLY)

! IV, ORAL, DERMAL, AND IP ROUTES OF ADMINISTRATION.

!MODEL TRACKS DISPOSITION OF NMP AND 5-HNMP.

!ASSUMPTIONS:

! (1) FLOW-LIMITED (ALL COMPARTMENTS)

! (2) METABOLISM OF NMP BY A SAT PATHWAY TO FORM 5HNP

! (3) METABOLISM OF HNP BY SATURABLE PATHWAY TO ETC.

! (5) METABOLISM OCCURS ONLY IN THE LIVER

! (6) TISSUE:BLOOD PART. COEFF. RAT = HUMAN = KRISHNAN EQN

! UPDATED IN CMD FILE TO MEASURED IN-HOUSE

! (7) 5HNP ELIMIN FROM MIXED VENOUS - 1ST ORDER

! THIS DIFFERS FROM 02: URINE BY *GFR CLEARANCE FROM KIDNEY

! METAB RATE CONST. FROM REPORT - UPDATED WITH LIT VALUES IN CMD FILE

! OTHER PARAMETERS CHANGED NOMINALLY TO HARMONIZE WITH FETAL IPA MODEL OF

! GENTRY ET AL. REGU TOX PHARM 36:51-68, 2002

! GENTRY MODEL NOTES:

! -CODING FOR PREGNANCY IS FROM MEHGFAT.CSL WITH SOME MINOR CHANGES

! -PHYSIOLOGICAL PARAMETERS ARE FROM MEHGFAT.CSL (AJUSTED AS NEEDED)

! -NON-PREGNANT MAMMARY TISSUE AND UTERINE VOLUME IS FROM ICRP

! -NON-PREGNANT MAMMARY TISSUE AND UTERINE BLOOD FLOWS ARE BASED ON THE

! - RATIOS OF MAMMARY AND UTERINE TISSUE VOLUMES TO RAPIDLY PERFUSED

! - TISSUE VOLUME AND BLOOD FLOW TO RAPIDLY PERFUSED TISSUE WHERE RAPIDLY

! - PERFUSED TISSUE INCLUDES LIVER, LUNG, ETC.

! - ((VMAMC/VRAPC)*QRAPC) AND ((VUTRC/VRAPC)*QRAPC)

! -DATA USED TO FIT CURVE FOR GROWING RAPIDLY PERFUSED TISSUE IN

! - MEHGFAT.CSL WAS REFIT SEPARATELY TO FIT CURVES FOR GROWING UTERUS

! - AND MAMMARY TISSUE IN THIS MODEL

! -BODY WEIGHT AND CARDIAC OUTPUT ARE CALCULATED AS THE INITIAL VALUES

! - PLUS THE CHANGE IN THE GROWING COMPARTMENTS

! -INCREASE IN BLOOD FLOW TO FAT, MAMMARY TISSUE, AND UTERUS ARE MODELED

! - AS BEING PROPORTIONAL TO THE INCREASE IN VOLUME IN THOSE COMPARTMENTS

! - BASED ON THE DATA IN THORESEN AND WESCHE, 1988 (UTERUS AND MAMMARY

! - TISSUE)

INITIAL

TABLE RESLVL, 1, 1441 / 1441*0.0, 1441*0.0 /

! HUMAN TOTAL PULMONARY VENTILATION RATE (L/HR FOR 1 KG ANIMAL)

CONSTANT QPC = 27.75

! HUMAN BLOOD FLOWS (FRACTION OF CARDIAC OUTPUT)

CONSTANT QCC = 12.9 ! CARDIAC OUTPUT (L/HR FOR 1 KG ANIMAL)

CONSTANT QFATC = 0.052 ! FAT (NON-PREGNANT FEMALE)

CONSTANT QLIVC = 0.227 ! LIVER

CONSTANT QMAMC = 0.027 ! MAMMARY TISSUE (NON-PREGNANT FEMALE)

CONSTANT QRAPC = 0.325 ! RAPIDLY PERFUSED

CONSTANT QSKC = 0.058 ! SKIN

CONSTANT QUTRC = 0.0062 ! UTERUS (NON-PREGNANT FEMALE)

! GENTRY MODEL HAS 0.249, BUT ADDING THESE =0.944, SO BE AWARE CAN REPLACE WITH EQN

! PERMEABILITY-AREA PRODUCT (L/HR)

CONSTANT PAFC = 0.01 ! DIFFUSION ON FETAL SIDE OF PLACENTA

! NOT SURE WHERE OPTIMIZED PARAMETER COMES FROM VISAVIS

GENTRY

! HUMAN TISSUE VOLUMES (FRACTION OF BODY WEIGHT)

CONSTANT BWINIT = 67.8 ! PRE-PREGNANCY BODY WEIGHT (KG)

CONSTANT VALVC = 0.0079 ! ALVEOLAR BLOOD

CONSTANT VBLC=0.06

CONSTANT VFATC = 0.273 ! FAT (NON-PREGNANT FEMALE)

CONSTANT VLIVC = 0.026 ! LIVER

CONSTANT VMAMC = 0.0062 ! MAMMARY TISSUE (NON-PREGNANT FEMALE)

CONSTANT VRAPC = 0.1044 ! RAPIDLY PERFUSED

!CONSTANT VSLWC = 0.35 ! SLOWLY PERFUSED IN GENTRY MODEL, THIS MODEL IS CALCULATED BELOW

CONSTANT VUTRC = 0.0014 ! UTERUS (NON-PREGNANT FEMALE)

CONSTANT VSKC=0.19

! HUMAN DERMAL EXPOSURE PARAMETERS

CONSTANT P = 0.0016 ! PERMEABILITY CONSTANT (KP) (CM/HR)

CONSTANT PV=31.0 ! PERMEABILITYT CONSTANT (CM/HR)

FOR VAPOR

!FOR PARENT MODEL, SKIN COMPARTMENT IS ONLY DEFINED AS DOSED SKIN

CONSTANT SAL = 0.01 !SURFACE AREA EXPOSED TO LIQUID, SQ.CM

CONSTANT SAV = 6700 !SURFACE AREA EXPOSED TO GAS/VAPOR, SQ.CM

CONSTANT HT=170.0 !HEIGHT (OR LENGTH) OF REFERENCE MAN

TSA = 71.81*(BWINIT**0.425)*(HT**0.725) !FOR HUMANS, DUBOIS AND DUBOIS, 1916, AS REPORTED IN REFERENCE MAN

VSKLC = VSKC*SAL/TSA

QSKLC = QSKC*SAL/TSA

VSKVC = VSKC*SAV/TSA

QSKVC = QSKC*SAV/TSA

! CONSTANT DERM=0 !DERMAL DOSE - MG (AMOUNT)

! DERM NOT USED IN REST OF CODE; PAUL SCHLOSSER, U.S. EPA (PS), 5-17-2013

CONSTANT FAD = 0.0 !FRACTION ABSORBED - FROM BADER ET AL, CALCULATE FROM AMNT
 REMAINING ON GAUZE
 CONSTANT PVL=0.0

! SLOWLY PERFUSED (DEFINED AS BALANCE OF TISSUES AND FLOWS)
 $VSLWC = 0.91 - (VFATC + VLIVC + VMAMC + VRAPC + VUTRC + VSKVC + VSKLC)$!VLUC + ! PMS 8-20-13,
 REMOVED + VALVC

! NOTE: 0.91 IS APPROX WHOLE BODY LESS BONE
 $VSLWC5 = 0.91 - (VFATC + VLIVC + VRAPC)$! PMS 8-20-13, REMOVED + VALVC
 $QSLWC = 1.0 - (QFATC + QLIVC + QMAMC + QRAPC + QUTRC + QSKVC + QSKLC)$
 $QSLWC5 = 1.0 - (QFATC + QLIVC + QRAPC) + QSKCC$

! MOLECULAR WEIGHTS
 CONSTANT MW=99.13 !MOL. WT. NMP, MG/MMOL
 CONSTANT MW1= 116.14 !MOL. WT. 5-HNP, MG/MMOL

STOCH = MW1/MW

! HUMAN NMP/BLOOD PARTITION COEFFICIENTS

!EXPERIMENTALLY MEASURED RATVALUES

CONSTANT PB = 450.0 ! BLOOD/AIR
 CONSTANT PFAT = 0.61 ! FAT
 CONSTANT PLIV = 1.00 ! LIVER
 CONSTANT PMAM = 1.0 ! MAMMARY TISSUE, ESTIMATED FROM LIVER
 CONSTANT PPLA = 0.31 ! PLACENTA
 CONSTANT PRAP = 1.0 ! RAPIDLY PERFUSED TISSUE, LIVER
 CONSTANT PSLW = 0.30 ! SLOWLY PERFUSED TISSUE, MUSCLE
 CONSTANT PUTR = 0.34 ! UTERUS
 CONSTANT PSKA = 44.5 !450.0 ! USE (BLOOD/AIR)*(RAT SKIN:LIQUID)/(HUMAN
 BLOOD:LIQUID)
 CONSTANT PSKL = 0.42 ! MEASURED SKIN;LIQUID (RAT)
 CONSTANT PSKB = 0.099 ! (RAT SKIN:LIQUID)/(HUMAN BLOOD:LIQUID)
 CONSTANT PLU = 0.1 ! LUNG:BLOOD

!METABOLIC RATE CONSTANTS

!**THESE ARE FROM PAYAN ET AL

!NMP TO 5HNP

CONSTANT KM=198.0 !MICHAELIS CONSTANT, MG/L
 CONSTANT VMAXC=2.67 !MAX. ENZ. ACT., MG/HR/L

! HUMAN 5HNMP TISSUE/BLOOD PARTITION COEFFICIENTS

! MEASURED

CONSTANT PB1=5.0
 CONSTANT PLIV1=3.0 ! LIVER MEASURED
 CONSTANT PFAT1=0.40 !MEASURED
 CONSTANT PRAP1=0.93
 CONSTANT PSLW1=0.40

!NO FETAL COMPARTMENT FOR METABOLITE, NMP IS CONSIDERED THE ACTIVE MOIETY

!5HNP TO OTHER METABS

CONSTANT KM2=22.8 !MICHAELIS CONSTANT, MG/L
 CONSTANT VMAX2C=1.0 !MAX. ENZ. ACT., MG/HR/L

! HUMAN UPTAKE AND CLEARANCE PARAMETERS

!URINARY ELIMINATION OF 5-HNMP - CLEARED FROM BLOOD

!NOTE FIRST ORDER RATE COMMENTED OUT, SATURABLE FITS BETTER

CONSTANT KAS=5.0

CONSTANT KME=8.0 !MICHAELIS CONSTANT, MG/L

CONSTANT VMAXEC=8.0 !MAX. ENZ. ACT., MG/HR/L

CONSTANT KMNE=8.0 !MICHAELIS CONSTANT FOR NMP IN URINE

CONSTANT VMXNEC=1.0

! INITIALIZE HUMAN CONCENTRATIONS IN TISSUES (MG/L)

CONSTANT ICART = 0.0 ! BLOOD

CONSTANT ICFAT = 0.0 ! FAT

CONSTANT ICLIV = 0.0 ! LIVER

CONSTANT ICRAP = 0.0 ! RAPIDLY PERFUSED

CONSTANT ICSKN = 0.0 ! SKIN

CONSTANT ICSLW = 0.0 ! SLOWLY PERFUSED

ICMAM = ICSLW ! MAMMARY TISSUE

ICUTR = ICRAP ! UTERUS

! DOSING PARAMETERS

CONSTANT CONCPPM = 0.0 ! INHALED CONCENTRATION (PPM)

CONSTANT CONCMGM = 0.0 ! INHALED CONCENTRATION (MG/M3)

CONSTANT IVDOSE = 0.0 ! IV DOSE (MG/KG)

CONSTANT PDOSE = 0.0 ! ORAL DOSE (MG/KG)

CONSTANT PDOSE2=0.0

CONSTANT PDOSE3=0.0

CONSTANT PDRINK = 0.0 ! DRINKING WATER DOSE (MG/KG/DAY)

CONSTANT TCHNG = 24.0 ! LENGTH INH. EXPOSURE OR IV INJ.(HRS)

CONSTANT DAYSWK = 5.0 ! NUMBER OF EXPOSURE DAYS PER WEEK

CONSTANT TMAX = 24.0 ! MAXIMUM TIME FOR EXPOSURES

CONSTANT S2=0.0

!INHALATION ON

CONSTANT P2=3.0

!INHALATION EXPOSURE

CONSTANT S3=3.16

!INHALTION

RESUME (HANOVER STUDY)

CONSTANT P3=3.0

!SECOND DAILY EXPOSURE PERIOD

CONSTANT ON3=1.0 ! SET TO ZERO TO TURN OFF 2ND DAILY PULSE; PMS 8-20-13

CONSTANT FULLWEEK=168.0 ! HRS IN A FULLWEEK; PMS 8-20-13

HRSWEEK=24.0*DAYSWK ! HRS/WEEK IN WORKPLACE; PMS 8-20-13

! STARTDS IS ADDED TO TCHNG TO ALLOW FOR DOSING THAT DOES NOT START AT T=0

!INITIAL EXPOSURE CONDITIONS

!DERMAL

```

    CONSTANT CONCL = 0.0      !CONC OF NMP IN LIQUID, MG/L
    CONSTANT SRATE = 0.0      ! MG/HR DELIVERED TO SKIN BY SPRAY
APPLICATION; PMS 8-20-13
    CONSTANT VLIQ = 1.0E-99   !INITIAL VOLUME APPLIED, L
    CONSTANT DENSITY=1.03
    CONSTANT RESID=0.0        !AMOUNT STICKING TO EXPOSURE SYSTEM, MG
    CONSTANT BRUSH=0.0        ! SET TO 1.0 FOR BRUSH/LIQUID
EXPOSURE; PMS 8-20-13
    DDN = CONCL*VLIQ
    !IN VITRO HUMAN VAN DYK ET AL. AIHA J 56: 651-660
    !START WITH SMALL SA SO VSKE IS NON-ZERO (USED IN DENOMINATOR OF CSK CALCULATION)

! EXPOSURE CONDITIONS BASED ON USER DEFINED INITIAL AMOUNTS OF CHEMICAL (MG)
    IF (CONCPPM.EQ.0.0) THEN
        CONCMG=CONCMGM/1000.0      !CONCERT MG/M3 TO
MG/L
    ELSE
        CONCMG = CONCPPM*MW/24451. !CONVERT PPM TO MG/LITER!
    ENDIF

!CONSTANT CONCMG=0
    !HANNOVER STUDY UNIT MG/M3 SO CONCMG /1000(L/M3)
CONSTANT DOSEINTERVAL=24.0      !TIME BETWEEN DAILY DOSES

! SIMULATION CONTROL PARAMETERS
    CONSTANT STARTDS = 0.0      ! TIME FIRST DOSE IS GIVEN (HRS)
    CONSTANT TSTOP = 6480.0     ! RUN SIMULATION FOR ABOUT 9 MONTHS
    CONSTANT CINTC = 0.1
    CONSTANT GDSTART = 0.0      ! GESTATION DAY ON WHICH SIMULATION STARTS; PMS
8-20-13

! SCALED HUMAN PULMONARY VENTILATION RATE (L/HR)
    QP = QPC * (BWINIT**0.75)
    QALV = 0.67 * QP

! SCALED HUMAN BLOOD FLOWS (L/HR)
    QCINIT = QCC * (BWINIT**0.75)
    QFATI = QFATC * QCINIT
    QLIV = QLIVC * QCINIT
    QMAMI = QMAMC * QCINIT
    QPLAI = 58.5 * VPLAI      ! VALUE FOR 'DAYS'=0 PER CALCULATION BELOW; PMS, 8-20-13
    QRAP = QRAPC * QCINIT
    QSLW = (QSLWC * QCINIT) - QPLAI ! - QSKCC ! QSKCC IS ALREADY SUBTRACTED IN SETTING QSLWC
ABOVE; PMS 8-20-13
    ! BUT INITIAL PLACENTAL BLOOD FLOW IS NOT, SO NOW SUBTRACTED
HERE; PMS 8-20-13
    ! QSLW5= (QSLWC5* QCINIT) ! WILL CALCULATE BY SUBTRACTION IN THE DERIVATIVE SECTION; PMS
8-1913

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QUTRI = QUTRC * QCINIT

QSKL = QSKLC * QCINIT

QSKV = QSKVC * QCINIT

! SCALED HUMAN TISSUE VOLUMES (L)

VALV = VALVC * BWINIT

!VFATI = VFATC * BWINIT

VFATI = BWINIT*(VFATC+(0.09*EXP(-12.90995862*EXP(-0.000797*24.0*GDSTART))))

VFETI = 3.50 * (EXP(-16.081*EXP(-5.67E-4*24.0*GDSTART))+ EXP(-140.178*EXP(-7.01E-4*24.0*GDSTART)))

!VMAMI = VMAMC * BWINIT

VMAMI = BWINIT*(VMAMC+(0.0065*EXP(-7.444868477*EXP(-0.000678*24.0*GDSTART))))

!VPLAI = 0.85*EXP(-9.434) ! VALUE FOR 'DAYS'=0 PER CALCULATION BELOW; PMS

8-19-13

VPLAI = 0.85*EXP(-9.434*EXP(-5.23E-4*24.0*GDSTART))

!VUTRI = VUTRC * BWINIT

VUTRI = BWINIT*(VUTRC+(0.02*EXP(-4.715669973*EXP(-0.000376*24.0*GDSTART))))

VLIV = VLIVC * BWINIT

VRAP = VRAPC * BWINIT

VSKL = VSKLC * BWINIT

VSKV = VSKVC * BWINIT

VBL=VBLC * BWINIT

VSLW = (VSLWC * BWINIT) ! - VSKCC; PMS 8-20-13

! VSLW5 = VSLWC5 * BWINIT ! NOW CALCULATED BY SUBTRACTION IN DERIVATIVE SECTION; PMS 8-20-13

! SCALED HUMAN METABOLISM PARAMETERS

VMAXE = VMAXEC*(BWINIT**0.75) !URINE 5HNMP

VMXNE=VMXNEC*(BWINIT**0.75) !URINE NMP

VMAX = VMAXC * (BWINIT**0.75)

VMAX1 = VMAX2C * (BWINIT**0.75)

! INITIALIZE HUMAN NMP AMOUNTS IN TISSUES

IAART = ICART * VALV

IAFAT = ICFAT * VFATI

IALIV = ICLIV * VLIV

IAMAM = ICMAM * VMAMI

IARAP = ICRAP * VRAP

IASKL = ICSKN * VSKL ! VSKCC ! PMS 8-20-13

IASKV = ICSKN * VSKV

IASLW = ICSLW * VSLW

IAUTR = ICUTR * VUTRI

INITTOT = IAART + IAFAT + IALIV + IAMAM + IARAP + IASKL + IASKV + IASLW + IAUTR

! INITIALIZE STARTING VALUES

BW = BWINIT

DRINK = (PDRINK * BW) / 24.0 ! DRINKING WATER DOSE (MG/HR)

```
CINT = CINTC
IV = 0.0
DAYEXP = 1.0
CINH = 0.0
CONSTANT FRACIN = 0.97  !FRACTIONAL UPTAKE OF NMP BY INHAL,START AT 65%
                           !OF ALVEOLAR - AS IN AKESSON ET AL 1997
CONSTANT FRACOR = 1.0  !FRACTION ABSORBED ORALLY, INITALLY 100%

! CONVERT ORAL DOSE FROM UG/KG TO UMOLES
! MODIFY DOSE TO ACCOUNT FOR FRACTIONAL ABSORPTION

ODOSE1= PDOSE * BW * FRACOR  ! UMOLES
ODOSE2= PDOSE2* BW * FRACOR  ! UMOLES
ODOSE3= PDOSE3* BW * FRACOR  ! UMOLES

CONSTANT TIME=0.0
CONSTANT TIME1 = 0.0  !'DAILY RAT EXPO (HR)'
CONSTANT TIME2 = 4.0  !'SECOND DAILY EXPOSURE (HR)'
CONSTANT TIME3 = 4.0  !'THIRD DAILY DOSE'
CONSTANT REPTM=720.0  ! CHANGE TO 24 FOR DAILY DOSING

SCHEDULE DOSE1 .AT. TIME1

DZONE = 1.0  ! START WITH EXPOSURE ON
SCHEDULE OFFD.AT.P2
SCHEDULE OND2.AT.24.0
IF (ON3) SCHEDULE OND3.AT.S3

END  ! END OF INITIAL

DYNAMIC
ALGORITHM IALG = 2  ! GEAR STIFF METHOD

DISCRETE DOSE1
ODOSE = ODOSE+ODOSE1
SCHEDULE DOSE2 .AT. (TIME+TIME2)
END

DISCRETE DOSE2
ODOSE = ODOSE+ODOSE2
SCHEDULE DOSE3 .AT. (TIME+TIME3)
END

DISCRETE DOSE3
ODOSE = ODOSE+ODOSE3
SCHEDULE DOSE1 .AT. (TIME+REPTM-TIME2-TIME3)
END
```

```

DISCRETE DOSEON  ! START DOSING
INTERVAL DOSEINT = 24.0      ! INTERVAL TO REPEAT DOSING
SCHEDULE DOSEOFF .AT. T + TCHNG
IF ((T.GE.STARTDS) .AND. (T.LT.TMAX)) THEN
    IF (T.LE.(STARTDS+TCHNG)) THEN
        IF (IVDOSE.GT.0.0) CINT = MIN(CINTC, (TCHNG/10.0))
        IV = (IVDOSE*BW) / TCHNG  ! RATE OF INTRAVENOUS DOSING (MG/HR)
    ENDIF
ENDIF
END ! DOSEON

DISCRETE DOSEOFF
CINH = 0.0
CINT = CINTC
IV = 0.0
END

DISCRETE OND2
DZONE=1.0
SCHEDULE OND2.AT.(T+24.0)
SCHEDULE OFFD.AT.(T+P2)
END

DISCRETE OND3
DZONE=1.0
SCHEDULE OND3.AT.(T+24.0)
SCHEDULE OFFD.AT.(T+P3)
END

!EXPOSURE CONTROL
DISCRETE OFFD
DZONE=0.0      !TURN OFF DERMAL
END

DERIVATIVE
HOURS = T
MINUTES = T * 60.0
DAYS = T / 24.0 + GDSTART  ! PMS 8-20-13, ADDED GDSTART
GTIME = T + GDSTART*24.0    ! PMS 8-20-13, REPLACES "T" IN TISSUE VOLUME CALCS
BELOW

! VOLUME OF HUMAN FAT (L)
VFAT = BWINIT*(VFATC+(0.09*EXP(-12.90995862*EXP(-0.000797*GTIME))))

! VOLUME OF HUMAN FETUS (L)
VFET = 3.50 * (EXP(-16.081*EXP(-5.67E-4*GTIME))+ EXP(-140.178*EXP(-7.01E-4*GTIME)))

! VOLUME OF HUMAN MAMMARY TISSUE (L)
VMAM = BWINIT*(VMAMC+(0.0065*EXP(-7.444868477*EXP(-0.000678*GTIME))))

```

! VOLUME OF HUMAN PLACENTA (L)

$$VPLA = 0.85 * \exp(-9.434 * \exp(-5.23E-4 * GTIME))$$

! VOLUME OF HUMAN UTERUS (L)

$$VUTR = BWINIT * (VUTRC + (0.02 * \exp(-4.715669973 * \exp(-0.000376 * GTIME))))$$

! INCREASE IN HUMAN BODY WEIGHT (KG)

$$BW = BWINIT + (VFAT - VFATI) + VFET + (VMAM - VMAMI) + VPLA + (VUTR - VUTRI)$$

! SCALED HUMAN ALVEOLAR VENTILATION (L/HR)

$$QP = QPC * (BW^{**0.75})$$

$$QALV = 0.67 * QP$$

! INCREASE IN HUMAN BLOOD FLOWS (L/HR)

$$QFAT = QFATI * (VFAT / VFATI)$$

$$QMAM = QMAMI * (VMAM / VMAMI)$$

$$QUTR = QUTRI * (VUTR / VUTRI)$$

! HUMAN BLOOD FLOW TO PLACENTA (L/HR)

$$QPLA = 58.5 * VPLA$$

! INCREASED HUMAN CARDIAC OUTPUT (L/HR)

$$! QC = QCINIT + (QFAT - QFATI) + (QMAM - QMAMI) + (QPLA) + (QUTR - QUTRI)$$

$$QC = QCINIT + (QFAT - QFATI) + (QMAM - QMAMI) + (QPLA - QPLAI) + (QUTR - QUTRI)$$

! NOW SUBTRACTING QPLAI ABOVE; PMS 8-20-13

$$QSLW5 = QC - (QFAT + QLIV + QRAP) \quad ! PMS, 8-20-13$$

$$VSLW5 = BW - (VFAT + VLIV + VRAP) \quad ! PMS, 8-20-13$$

! SCALED PERMEABILITY-AREA PRODUCT

$$PAF = PAFC * (VFET^{**0.75})$$

! ----- HUMAN NMP MODEL -----

! AMOUNT EXHALED (MG)

$$RAEXH = QALV * CALV$$

$$AEXH = \text{INTEG}(RAEXH, 0.0)$$

$$CI = \text{CONCMG} * CZONE + \text{RESLVL}(T)$$

! FOR A 5 DAY/WK EXPOSURE, CHANGE FIRST PULSE TO PULSE(0,7*24,5*24)

! FOR DAILY, PULSE(0,1E6,24)

$$TORAL = ODOSE1 - AO \quad ! \text{AMT ABSORBED ORALLY, MG!}$$

$$RSTOM = -KAS * AO$$

$$RAO = KAS * AO \quad ! \text{CHANGE IN STOMACH (UMOLE/HR)}$$

$$AO = ODOSE1 + \text{INTEG}(RSTOM, 0.0) \quad ! \text{AMT IN STOMACH (UMOLE)}$$

! AMOUNT IN FAT (MG)

$$\text{RAFAT} = \text{QFAT} * (\text{CART} - \text{CVFAT})$$

$$\text{AFAT} = \text{INTEG}(\text{RAFAT}, \text{IAFAT})$$

$$\text{CFAT} = \text{AFAT} / \text{VFAT}$$

$$\text{CVFAT} = \text{CFAT} / \text{PFAT}$$

! AMOUNT IN FETUS (MG)

$$\text{RAFET} = \text{PAF} * (\text{CPLA} - \text{CFET})$$

$$\text{AFET} = \text{INTEG}(\text{RAFET}, 0.0)$$

$$\text{CFET} = \text{AFET} / \text{VFET}$$

$$\text{AUCCFET} = \text{INTEG}(\text{CFET}, 0.0)$$

! AMOUNT IN LIVER (MG)

$$\text{RALIV} = (\text{QLIV} * (\text{CART} - \text{CVLIV})) + \text{RAO} + \text{DRINK} - \text{RAMET1}$$

$$\text{ALIV} = \text{INTEG}(\text{RALIV}, \text{IALIV})$$

$$\text{CLIV} = \text{ALIV} / \text{VLIV}$$

$$\text{CVLIV} = \text{CLIV} / \text{PLIV}$$

! AMOUNT METABOLISED IN LIVER -- SATURABLE (MG)

$$\text{RAMET1} = (\text{VMAX} * \text{CVLIV}) / (\text{KM} + \text{CVLIV})$$

$$\text{AMET1} = \text{INTEG}(\text{RAMET1}, 0.0)$$

! AMOUNT IN MAMMARY TISSUE (MG)

$$\text{RAMAM} = \text{QMAM} * (\text{CART} - \text{CVMAM})$$

$$\text{AMAM} = \text{INTEG}(\text{RAMAM}, \text{IAMAM})$$

$$\text{CMAM} = \text{AMAM} / \text{VMAM}$$

$$\text{CVMAM} = \text{CMAM} / \text{PMAM}$$

! AMOUNT IN PLACENTA (MG)

$$\text{RAPLA} = (\text{QPLA} * (\text{CART} - \text{CVPLA})) + (\text{PAF} * (\text{CFET} - \text{CPLA}))$$

$$\text{APLA} = \text{INTEG}(\text{RAPLA}, 0.0)$$

$$\text{CPLA} = \text{APLA} / \text{VPLA}$$

$$\text{CVPLA} = \text{CPLA} / \text{PPLA}$$

! AMOUNT IN RAPIDLY PERFUSED TISSUE (MG)

$$\text{RARAP} = \text{QRAP} * (\text{CART} - \text{CVRAP})$$

$$\text{ARAP} = \text{INTEG}(\text{RARAP}, \text{IARAP})$$

$$\text{CRAP} = \text{ARAP} / \text{VRAP}$$

$$\text{CVRAP} = \text{CRAP} / \text{PRAP}$$

!ASKL = AMOUNT NMP IN LIQUID-EXPOSED SKIN TISSUES (MG) AND DERMAL DOSING (FROM VAPOR)

! EQUATIONS BELOW SET FOR LIQUID-EXPOSED SKIN, PMS 8-21-13

$$\text{RASKL} = \text{QSKL} * (\text{CART} - \text{CVSKL}) + \text{RADVL} + \text{RASL}$$

$$\text{ASKL} = \text{INTEG}(\text{RASKL}, 0.0)$$

! CVSKL = ASKL/VSKL ! (VSKCC) ! PMS 8-20-13

! CSKL = CVSKL/PSKL ! 'NMP IN SKIN, MG/L'

CSKL = ASKL/VSKL ! (VSKCC) ! CALCULATION OF VENOUS BLOOD AND TISSUE CONCNS WAS

REVERSED; PMS 8-21-13

CVSKL = CSKL/PSKB ! 'NMP IN SKIN, MG/L'

```

!CVSK3 = CVSK*1000/MWNMP  !'NMP IN CVSK, MICROMOL/L'
CZONE = PULSE(0.0,FULLWEEK,HRSWEEK)*DZONE ! PMS 8-20-13
! FOR A 5 DAY/WK EXPOSURE, USE FULLWEEK=7*24, HRSWEEK=5*24 (DAYSWK=5)
! FOR A SINGLE DAY, FULLWEEK=1E16, HRSWEEK=24 (DAYSWK=1)
SDELIV=SRATE*CZONE ! CONSTANT-RATE SPRAY DELIVERY; PMS 8-20-13
! SPRAY-DERMAL EXPOSURES, ASSUMED SIMULTANEOUS WITH INHALATION
RADVL = (PV*SAL/1000.0)*(CI - (CSKL/PSKA))*(1.0-CZONE)*(SDELIV.EQ.0.0) + SDELIV
! RADV ALLOWS ABSORPTION/DESORPTION FROM AIR WHEN THERE IS
NOT SPRAY OR
! BRUSHING DERMAL EXPOSURE, WHEN BOTH SDELIV AND DZONE ARE
ZERO; PMS 8-20-13
ADVL = INTEG(RADVL,0.0)  !'AMT NMP ABSORBED DERMAL,MG'

CONCL2=CONCL*FAD
CSURF=CONCL2-(ADSL/VLIQ) ! FOR APPLICATIONS WITH NEAR-CONSTANT CSURF, SET VLIQ=1E9 OR
HIGHER; PMS 8-2-13
RASL=(PVL*SAL/1000.0)*(CSURF-(CSKL/PSKL))*CZONE*BRUSH
!RASL=((PVL*SA/1000)*CSURF)-(CVSK/PSKL)
ADSL=INTEG(RASL,0.0)

!ASKV = AMOUNT NMP IN VAPOR-EXPOSED SKIN TISSUES (MG) AND DERMAL DOSING (FROM VAPOR);
PMS 8-21-13
RASKV = QSKV*(CART - CVSKV) + RADVV
ASKV = INTEG(RASKV,0.0)
! CVSKV = ASKV/VSKV ! (VSKCC) ! PMS 8-20-13
! CSKV = CVSKL/PSKV !'NMP IN SKIN, MG/L'

CSKV = ASKV/VSKV ! (VSKCC) ! PMS 8-20-13
CVSKV = CSKV/PSKB !'NMP IN SKIN, MG/L'
!CONCDERM=CONCMG* PULSE(0,1E6,24)*(PULSE(S2,24,P2)+ PULSE(S3,24,P3))
! RADVV = (PV*SA/1000.0)*(CONCDERM - (CVSKV/PSKA))*DZONE
RADVV = (PV*SAV/1000.0)*(CI - (CSKV/PSKA))
ADV = INTEG(RADVV,0.0)  !'AMT NMP ABSORBED DERMAL,MG'

! AMOUNT IN SLOWLY PERFUSED TISSUE (MG)
RASLW = QSLW * (CART - CVSLW)
ASLW = INTEG(RASLW, IASLW)
CSLW = ASLW / VSLW
CVSLW = CSLW / PSWL

! AMOUNT IN UTERUS (MG)
RAUTR = QUTR * (CART - CVUTR)
AUTR = INTEG(RAUTR, IAUTR)
CUTR = AUTR / VUTR
CVUTR = CUTR / PUTR

! BLOOD VENOUS ARTERIAL (C)
CVEN=(QFAT*CVFAT + QLIV*CVLIV + QMAM*CVMAM + QPLA*CVPLA + QRAP*CVRAP + QSLW*CVSLW &
+ QUTR*CVUTR + QSKV*CVSKV + QSKL*CVSKL + IV) / QC

```

!(QFAT + QLIV + QMAM + QPLA + QRAP + QSLW+ QUTR + QSKV + QSKL) / QC
 ! TOTAL VENOUS BLOOD
 !RABL= QC * (CVEN - CART) ! RATE OF CHANGE IN MIXED BLOOD
 !ABL= INTEG(RABL,0.0) ! AMOUNT IN MIXED BLOOD
 ! ABOVE NOT USED; PMS 8-21-13

! AMOUNT IN ARTERIAL BLOOD (MG)
 RABLD = QALV*(CI*FRACIN - CALV) + QC*(CVEN-CART) - RAUNP
 ABLD = INTEG(RABLD, IAART)
 CART = ABLD / VBL
 CALV = CART / PB
 CALVPPM = CALV * 24450.0 / MW
 AUCCBLD = INTEG(CART, 0.0)

! AMOUNT IN URINE (MG)
 !RAUNP = KLN*CART !FIRST ORDER RATE OF LOSS (URINE
 RAUNP = VMXNE*CART/(KMNE+CART) !SATURABLE ELIMINATION
 AUNP = INTEG(RAUNP,0.0)

! ----- HUMAN 5HNMP MODEL -----

! AMOUNT EXHALED (MG)
 ! RAEXH1 = QALV * CALV1
 ! AEXH1 = INTEG(RAEXH1, 0.0)
 ! CALVPPM1 = CALV1 * (24450.0 / MW1)

! AMOUNT IN FAT (MG)
 RAFAT1 = QFAT * (CART1 - CVFAT1)
 AFAT1 = INTEG(RAFAT1, 0.0)
 CFAT1 = AFAT1 / VFAT
 CVFAT1 = CFAT1 / PFAT1

! AMOUNT IN LIVER (MG)
 RALIV1 = ((QLIV * (CART1 - CVLIV1)) + (RAMET1*STOCH)) - RAMETM1
 ALIV1 = INTEG(RALIV1, 0.0)
 CLIV1 = ALIV1 / VLIV
 CVLIV1 = CLIV1 / PLIV1

! AMOUNT METABOLISED IN LIVER -- SATURABLE (MG)
 RAMETM1 = (VMAX1 * CVLIV1) / (KM2 + CVLIV1)
 AMETM1 = INTEG(RAMETM1, 0.0)

! AMOUNT IN RAPIDLY PERFUSED TISSUE (MG)
 RARAP1 = QRAP * (CART1 - CVRAP1)
 ARAP1 = INTEG(RARAP1, 0.0)
 CRAP1 = ARAP1 / VRAP
 CVRAP1 = CRAP1 / PRAP1

! AMOUNT IN SLOWLY PERFUSED TISSUE (MG)

```

RASLW1 = (QSLW5) * (CART1 - CVSLW1)
ASLW1 = INTEG(RASLW1,0.0)
CSLW1 = ASLW1 / VSLW5
CVSLW1 = CSLW1 / PSLW1

! CONCENTRATION IN MIXED VENOUS BLOOD (MG/L)
CVEN1 = (QFAT*CVFAT1 + QLIV*CVLIV1 + QRAP*CVRAP1 + QSLW5*CVSLW1)/QC
RART1 = QC*(CVEN1-CART1)-RAUHP
ABLD1=INTEG(RART1,0.0)
CART1 = ABLD1/VBL

! AMOUNT IN ARTERIAL BLOOD (MG)
!CALV1 = CART1 / PB1
AUCCBLD1 = INTEG(CART1, 0.0)

! AMOUNT IN URINE (MG)
RAUHP = VMAXE*CART1/(KME+CART1) !SATURABLE ELIMINATION
!RAUHP=KLC*CART1
AUHP = INTEG(RAUHP,0.0)

INHALTOT=INTEG((QALV*(CI*FRACIN - CALV)), 0.0)
IVTOT=INTEG(IV, 0.0)

! ----- CHECK MASS BALANCE -----
INTOT=INTEG((QALV*CI*FRACIN), 0.0)
! NEW SKIN TERMS ADDED BELOW; PMS 8-21-13
TDOSE = INTOT + AO + INITTOT+TORAL+ADSL+ADVL+ADVW !+ INTEG(IV, 0.0)
NMPTOT = ABLD + AFAT + AFET + ALIV + AMAM + APLA + ARAP + ASKL + ASKV + ASLW + AUTR + AEXH
+ AUNP + AMET1
MASSBAL = TDOSE/(NMPTOT+0.000000000001)

TERMT(T.GT.TSTOP, 'SIMULATION FINISHED')

END          ! END OF DERIVATIVE

TERMINAL
DAUCCBLD = (AUCCBLD / TSTOP) * 24.0
DAUCCBLD1 = (AUCCBLD1 / TSTOP) * 24.0
DAUCTOT = DAUCCBLD + DAUCCBLD1

DAUCCFET = (AUCCFET / TSTOP) * 24.0
DAUCTFET = DAUCCFET
END

END          ! END OF DYNAMIC
END          ! END OF PROGRAM

```

RATPARAMS.M

WESITG=0; WEDITG=0;
VCHC=1e9, KLOSS=0.0, DOSE=0, TINF=0.01, PDOSE=0, DOSE2=0, CONCCHPPM0 = 0
CONCL=0, IVDOSE=0, TCHNG=999.0, TSTOP=120, CONCPM=0, CONCMGS=0, DSK=0
%FAD=0.76 % Value from Payanderm.m; should only effect dermal exposure; PS 5-1-13
FAD=1 % From Poet 5-16-13 Payanderm.m file; PS 5-17-13
GDDAYS=0, SA=0.00001, DOSEINTERVAL=720, CINT=1, VLIQ=1e-99,
FRACIN=1 %1E-55 % Changed to 1 to match ghantinahladata.m value; should not change w/ exposure
route; PS 5-1-13
NUMFET=0.01 % Added to minimize impact on other volumes; Paul Schlosser (PS), U.S. EPA, 05-01-2103
KAS=1.36, FRACOR=0.68
% KPL=0.0000016
%KPL=4.3e-3 % Value from Payanderm.m; should only effect dermal exposure; PS 5-1-13
KPL=4.6e-3 % From Poet 5-16-13 Payanderm.m file; PS 5-17-13
VLIVC=0.0366
VLUC=0.005
VFATC=0.09
VRAPC=0.071
QLIVC=0.183
QPC=16.0
QCC=16.0
QFATC=0.07
QSKNC=0.058
QMAMC=1e-5
QUTRC=1e-5
KM=234
VMAXC=21.8
KM2=48
VMAX2C=2.4
QSC=0.14
BWINIT=0.23
GDDAYS=0
GDMONTHS=0
KLC=3.9
KLNC=0.0019
PAFC=0
MAXT=1e-2
MINT=1E-9

QFATC = 0.072
QLIVC = 0.183
QMAMC = 0.001
QSKNC = 0.058
QUTRC = 0.001
QRAPC = 0.512

VLUC = 0.007

VFATC = 0.10
VLIVC = 0.034
VMAMC = 0.01
VRAPC = 0.071
VUTRC = 0.002
VBLC = 0.067

PB=450.0
PF=0.62
PL=1.02
PR=1.02
PS=0.74
PLU=0.10

%PSKA= 450.0 %Air-skin transport equations, where PSKA appears, are commented
% out in Poet 5-15-13 NMPpreg_rat.m; PS 5-17-13

%PSK=150

PSKL = 0.42 % MEASURED % 450 % Value for Poet 5-16-13 Payanderm.m file; PS 5-17-13

PSKB = 0.12 % SKIN:SALINE/BLOOD:SALINE

PSKA = 55 % SKIN:SALINE*BLOOD:AIR/BLOOD:SALINE

PM=1.0

PPLA=0.309

PUTR=0.34

PLHNP=3.0

PBHNP=0.73

PFHNP=0.40

PPLHNP=01.07

PREG_RAT_PARAMS.M

% To assure parameter consistency, calling ratparam first below and

% commenting out redundant setting of parameters here.

% Paul Schlosser, U.S. EPA , 05-01-2013

ratparam

% VCHC=1.0E+9, KLOSS=0.0, DOSE=0, TINF=0.01, PDOSE=0 % set in ratparam

% CONCL=0, IVDOSE=0, TCHNG=999.0, TSTOP=120, CONCPPM=0, CONCMGM=0

% GDDAYS=6, SA=0.00001, DOSEINTERVAL=720

QUTRC=0.005, %QRAPC=0.512

VLIVC=0.0366, VLUC=0.005, VFATC=0.09, %VRAPC=0.071, QLIVC= 0.183,

QPC=15, QCC=15, % These are both 16 in ratparam; PS 5-1-13

%QFATC=0.07, QSKNC=0.058 % set in ratparam

% KM=234, VMAXC=21.8, KM2=48, VMAX2C=2.1 % set in ratparam

BWINIT=0.235, GDDAYS=6, %GDMONTHS=0

% KLC=3.9, KLNC=0.002, % set in ratparam

PAFC=0.1, NUMFET=7

NUMFET=14, PUPBW=5670 % Taken from pregparamsoutput.m

%MAXT=1.0e-4

%MINT=1E-9, VUTRC=0.002, VMAMC = 0.01 % set in ratparam

%PAFC OF 0.1 IS NEAR MAX TRANSFER SEE GRAPHPAD PAF EFFECT 11 08

FIG_1_WELLS_1988_IV_PLASMA.M

```
%PROCED WELLS - IV
```

```
%WELLS AND DIGENIS 1988
```

```
prepare @all @clear
```

```
ratparam
```

```
DOSE=0,PDOSE=0,TCHNG=0.0083,TINF=0.0083,CINT=0.01
```

```
BWINIT=0.35, IVDOSE=45, TSTOP=24,GDDAYS=0
```

```
!!start/nc
```

```
MASBAL
```

```
% DATA WELLS (T,CV,Poet 2013 CV)
```

```
DWELLS = [0.08 90 65.59071
```

```
0.17 70 65.59071
```

```
0.25 60 64.07336
```

```
0.33 58 62.9852
```

```
0.50 56 60.90279
```

```
0.75 58 58.0206
```

```
1.00 52 55.2812
```

```
1.50 52 50.15439
```

```
2.0 50 45.45177
```

```
4.0 40 30.32493
```

```
6.0 35 19.94611
```

```
];
```

```
plot(_t, _cv, DWELLS(:,1), DWELLS(:,2), DWELLS(:,1), DWELLS(:,3),'Fig 2 Wells 1988 IV plasma.aps')
```

FIG_2_PAYAN_2002_IV_PLASMA.M

```
%PROCED WELLS - IV
```

```
%WELLS AND DIGENIS 1988
```

```
prepare @all @clear
```

```
ratparam
```

```
DOSE=0,PDOSE=0,TCHNG=0.0083,TINF=0.0083,CINT=0.01
```

```
BWINIT=0.35, IVDOSE=0.1, TSTOP=24,GDDAYS=1
```

```
!!start/nc
```

```
MASBAL
```

```
% DATA PAYAN (T,CV,Poet 2013 CV)
```

```
DPAYAN = [0.020.155 0.2573098
```

```
0.08 0.131 0.1561921
```

```
0.17 0.118 0.1433084
```

```
0.5 0.115 0.131193
```

```
1 0.112 0.1162329
```

```
1.5 0.109 0.1030575
```

```
2 0.103 0.09138391
```

```
3 0.093 0.07185712
```

```
4 0.06 0.05650498
```

```
];
```

```
plot(_t,_cv, DPAYAN(:,1), DPAYAN(:,2), DPAYAN(:,1), DPAYAN(:,3),'Fig 2 Payan 2002 IV plasma.aps')
```

FIG_3AB_PAYAN_2002_IV_5HNMP_PLASMA_URINE.M

prepare @all @clear

ratparam

% Commenting out items below set identically in ratparam; Paul Schlosser, U.S. EPA, 05-01-2013

%VCHC=1.0E+9, KLOSS=0.0, DOSE=0,TINF=0.01

% CONCL=0, IVDOSE=0,

TCHNG=0.01,TSTOP=78

% GDDAYS=0, SA=0.00001,CONCPPM=0,CONCMGM=0

BWINIT=0.25,CINT=0.1

IVDOSE=0.1

!!START /nc

holdcvhp=[_t_cvhp];

holdauhp=[_t_auhp];

IVDOSE=1

!!START /nc

holdcvhp=[holdcvhp_cvhp];

holdauhp=[holdauhp_auhp];

IVDOSE=10

!!START /nc

holdcvhp=[holdcvhp_cvhp];

holdauhp=[holdauhp_auhp];

IVDOSE=100

!!START /nc

holdcvhp=[holdcvhp_cvhp];

holdauhp=[holdauhp_auhp];

IVDOSE=500,BWINIT=0.275

!!START /nc

holdcvhp=[holdcvhp_cvhp];

holdauhp=[holdauhp_auhp];

% DATA p5HNMP (T,CVHP,Poet 2013 CVHP)

p5HNMP = [0.01	0.000182	0.001615	0.015095	0.099633	0.207601
5	0.042203	0.422267	4.237931	39.48625	109.9071
10	0.02516	0.252532	2.613575	31.12196	133.5288
20	0.004531	0.045548	0.478971	7.101832	69.10229
30	0.000617	0.006203	0.065172	0.993501	15.54205
40	0.0000752	0.000756	0.007927	0.119737	2.215258
50	0.00000867	0.000087	0.000911	0.013623	0.27038

```
60    0.000000966    0.00000969    0.000101    0.001503    0.031528
70    0.000000105    0.00000106    0.000011    0.000163    0.0036
];
```

% DATA u5HNMP (T,AUHP,Poet 2013 AUHP)

```
u5HNMP = [0.01    1.19E-08    0.00000009    0.00000084    0.00000606    0.0000154
5    0.003922    0.039152    0.384723    3.146931    8.153724
10   0.008028    0.08031    0.804688    7.576738    24.42693
20   0.011128    0.111449    1.130311    11.91568    52.64661
30   0.011648    0.116677    1.185414    12.75838    63.2357
40   0.011719    0.117399    1.19301    12.87606    65.35392
50   0.011729    0.11749    1.193972    12.89082    65.65677
60   0.01173    0.117501    1.194088    12.89259    65.6955
70   0.01173    0.117503    1.194102    12.8928    65.70028
];
```

% DATA payanPlas (T,CVHP,Payan 2002 CVHP)

```
payanplas = [1    0.00061    NaN    NaN    NaN    NaN
1.5    0.00055    NaN    NaN    NaN    NaN
2    0.00161    NaN    NaN    NaN    NaN
3    0.00398    NaN    NaN    NaN    NaN
4    0.0251    0.376    3.28    NaN    NaN
6    0.0341    NaN    NaN    NaN    NaN
8    0.0187    NaN    NaN    23.5    NaN
10   0.0095    NaN    NaN    NaN    NaN
24   0.00007    NaN    NaN    NaN    46.9
];
```

% DATA payanUrin (T,AUHP,Payan 2002 AUHP)

```
payanurin = [4    0.0009    0.0153    0.164    0.725    4.83
8    0.005    0.0507    0.591    2.473    10.29
24   0.0123    0.1213    1.27    13.62    54.77
48   0.0127    0.12608    1.29    12.22    63.94
72   0.0128    0.12742    1.298    12.35    64.38
];
```

```
plot(holdcvhp(:,1),holdcvhp(:,2:6),p5HNMP(:,1), p5HNMP(:,2:6),payanplas(:,1), payanplas(:,2:6), 'Fig 2
Payan 2002 IV plasma 5HNMP.aps')
plot(holdauhp(:,1),holdauhp(:,2:6),u5HNMP(:,1), u5HNMP(:,2:6),payanurin(:,1), payanurin(:,2:6), 'Fig 2
Payan 2002 IV urine 5HNMP.aps')
```

FIG_4_PAYAN_2003_DERMAL_PLASMA.M

prepare @all @clear

%ratparams

ratparam % Added by Paul Schlosser (PS), U.S. EPA, to assure parameter consistency; 05-01-2013

%preg_rat_params

%payan dermal exposures: Payan et al. DMD 03

% DOSE=0,PDOSE=0, % Commented out, PS 5-1-13

TCHNG=72,TSTOP=54, SA=10,VLIQ=200e-6

BWinit=0.250 % BWinit was 0.275; reset from Poet 5-16-13 Payenderm.m; PS 5-17-13

% CONCL=1030, FAD=0.76,PSK=150 %FAD - urine+carcas+tissues

CONCL=1050000, CINT=0.5 % from Poet 5-16-13 Payenderm.m; PS 5-17-13

% PSK and FAD (now) set in ratparam to assure cosnsitency; PS 5-1-13

%KPL=4.3e-3 % Moved to ratparam file, PS 5-1-13

!!START /nc

holdauhp=[_t _auhp];

holdaunp=[_t _aunp];

holdca=[_t _cv];

holdch=[_t _cvhp];

holdcsurf=[_t _csurf];

% Commenting out of following lines based on Poet 5-16-13 Payenderm.m; PS 5-17-13

%BWinit=0.275,CONCL=1030,VLIQ=0.000400

% !!START /nc

% holdauhp=[holdauhp _auhp];

%holdaunp=[holdaunp _aunp];

%holdca=[holdca _cv];

%holdch=[holdch _cvhp];

%holdcsurf=[holdcsurf _csurf];

MASBAL

% DATA pNMP (T,Payan 2013 CV)

pNMP = [0.5 128.652

2.5 424.496

5 532.623

7.5 508.955

10 434.405

12.5 346.867

15 263.728

17.5 192.406

20 179.829

22.5 99.759

25 63.993

27.5 34.099

30 17.645

32.5 8.97

35 4.516

```

37.5    2.262
40      1.13
42.5    0.564
45      0.282
47.5    0.141
50      0.0701
50.5    0.061
51      0.0531
51.5    0.0462
52      0.0402
52.5    0.035
55      0.0175
57.5    0.00874
60      0.00437
];

```

```
% DATA PAYAN (T, Payan 2003 CVHP)
```

```
PAYAN = [0.51 160
```

```

0.87    260
1.6     330
1.84    410
2.57    440
2.81    490
3.18    510
3.78    550
4.63    540
5.85    540
7.8     530
9.74    490
23.7    100
25.7    110
29.9    60
47.9    0
54.2    0
];

```

```
%plot(holdcsurf(:,1),holdcsurf(:,2), 'figcsurf.aps')
```

```
%plot(holdauhp(:,1),holdauhp(:,2), 'figDERMALAUHP.aps')
```

```
%plot(holdaunp(:,1),holdaunp(:,2), 'figDERMALAUnP.aps')
```

```
plot(holdca(:,1),holdca(:,2), pNMP(:,1), pNMP(:,2), PAYAN(:,1), PAYAN(:,2), 'Fig 7 Payan 2003 Dermal plasma.aps')
```

```
%plot(holdch(:,1),holdch(:,2), 'figDERMALplasmahp.aps')
```

HUMAN_PARAMS.M

```

WESITG=0; WEDITG=0;
SRATE=0; RESLVL=[zeros(1,1441) (0:1440)]';
QPC    =    15;
QLIVC  =    0.25;
QSKC   =    0.058;
BWINIT =    58;
VFATC  =    0.23;
VRAPC  =    0.042;
P       =    0.0036;
HT      =    180;
KAS     =    1.36;
ICFAT   =    0;
ICSKN   =    0;
CONCMGM =    0;
PDOSE2=    0;
TCHNG  =    8;
S2 = 0; P2    =    8;
S3      =    6720; P3    =    6720; ON3=0;
DENSITY =    1.03; VLIQ    =    1.00e-99; BRUSH=0;
STARTDS =    0;
FRACIN  =    1;
TIME1   =    8;
REPTM   =    24;
NSTP    =    10;
QCC     =    15;
QMAMC   =    0.027;
QUTRC   =    0.005;
VALVC   =    0.0079;
VLIVC   =    0.031;
VUTRC   =    0.0014;
PV       =    32;
MW       =    99.13;
KM2      =    50.5;
VMAX2C   =    5.9;
VMAXC   =    125;
KM       =    151;
KME      =    80.8;
VMXNEC   =    0.011;
KMNE     =    2.46;
VMAXEC   =    7.3;
ICLIV    =    0;
ICSLW    =    0;
IVDOSE   =    0;
PDOSE3=    0;
DAYSWK   =    1; % Days per week of exposure, eg 5 for workplace; PMS 8-28-13

CONCL    =    0;

```

RESID = 0;
 TSTOP = 24;
 FRACOR = 0.68;
 TIME2 = 6720;
 CINT = 0.1;
 MAXT = 0.001;
 QFATC = 0.05;
 QRAPC = 0.48;
 PAFC = 0.1;
 VBLC = 0.06;
 VMAMC = 0.0062;
 VSKC = 0.051;
 SAL = 0.0001;
 SAV = 6700;
 MW1 = 116.14;
 ICRAP = 0;
 CONCPPM = 0;
 PDOSE = 0;
 PDRINK = 0;
 TMAX = 24;

PVL=2.7e-3; % Added per Poet 5-16-13 human_params.m; Paul Schlosser, U.S. EPA (PMS), 5-17-13

% DOSEINTERVAL = 24; % Not used, PMS 8-28-13

DOSEINT=999;

CINTC = 0.1;
 TIME = 0;
 TIME3 = 6720;
 IALG = 2;
 MINT = 1.00e-09;
 PB = 450;
 PMAM = 1;
 PSLW = 0.77;
 PSKL = 0.42 % Rat skin:saline, PMS 8-28-13
 PSKB = 0.099 % (Rat skin:saline)/(human blood:saline), PMS 8-28-13
 PSKA = 44.5 %use (blood/air)*(rat skin:liquid)/(human blood:liquid), PMS 8-28-13
 % PSKA = 450 %750; Changed per Poet 5-16-13 human_params.m; PMS 5-17-13
 PBHNP = 0;
 PLIV = 0.82;
 PRAP = 0.94;
 PLIV1 = 2.5;
 PRAP1 = 6.5;
 ICART = 0;
 PSLW1 = 0.08;
 PFAT = 0.49;
 PPLA = 0.31;
 PUTR = 0.1;
 PLU = 0.1;
 PB1 = 1;
 PFAT1 = 0.23;

%FAD=0.000001

FAD = 1 % Value used in Poet 5-16-13 BADER_DRM.m and AkkesDerm.m; PMS 5-17-13

%DERM=0 % Not used in Poet 5-16-13 'HumPregRetrieve Restored 1.csl'; PMS 5-17-13

VCHC=1.0e+9; KLOSS=0.0; % From human simulation scripts; use as default for human; PMS 8-28-13

start @nocallback

POET_2013_FIG_5_AND_6.M

human_params

P2=3; S3=3.169; P3=3; ON3=1; DAYSWK=1;

BWINIT=79; HT=180; TSTOP=48;

% Poet 2013 Inhalation plasma NMP (T, 80mg CVEN, 39mg CVEN, 9.7 mg CVEN)

PLAS_NMP = [1 0.683103 0.332836 0.082749

2	1.024672	0.499001	0.12401
4	1.378491	0.670665	0.166542
6	1.661011	0.807381	0.200346
8	0.870433	0.422351	0.104658
10	0.476452	0.230971	0.057195
12	0.260598	0.126264	0.031254
14	0.14247	0.069009	0.017078
16	0.077869	0.037711	0.009332
18	0.045205	0.02189	0.005416
20	0.024702	0.011961	0.002959

];

% Poet 2013 Inhalation plasma NMP (T, 80mg CVEN1, 39mg CVEN1, 9.7 mg CVEN1)

PLAS_5HNMP = [1 0.24528 0.119668 0.02978

2	0.654421	0.319214	0.079424
4	1.63541	0.796202	0.197813
6	2.698992	1.309727	0.324586
8	3.13353	1.511975	0.373107
10	2.989524	1.433702	0.352195
12	2.622757	1.250767	0.306007
14	2.196787	1.042511	0.25417
16	1.78852	0.845258	0.205485
18	1.42952	0.673285	0.163293
20	1.128456	0.530008	0.128301
30	0.316655	0.147623	0.035559
40	0.084532	0.039321	0.009458

];

% Poet 2013 Inhalation plasma NMP (T, 80mg AUNP, 39mg AUNP, 9.7 mg AUNP)

URIN_NMP = [1 0.062401 0.038817 0.012091

2	0.152052	0.100311	0.033677
4	0.322807	0.223295	0.080098
6	0.538127	0.383801	0.144246
8	0.70041	0.501467	0.189331
10	0.83527	0.588113	0.217245
12	0.923142	0.638799	0.231732
14	0.97874	0.668416	0.239602
16	1.006836	0.682649	0.243234
18	1.019841	0.68907	0.244841
20	1.026145	0.692145	0.245604
30	1.031765	0.694865	0.246275

40 1.031889 0.694925 0.24629
];

% Poet 2013 Inhalation urine 5HNMP (T, 80mg AUHP, 39mg AUHP, 9.7 mg AUHP)

URIN_5HNMP = [1 0.275716 0.134652 0.033533
2 1.463359 0.715887 0.178497
4 6.268797 3.0758 0.768508
6 16.61853 8.177778 2.047459
8 16.61853 8.177778 2.047459
10 41.92996 20.65742 5.175538
12 54.71574 26.91465 6.735197
14 66.35912 32.57506 8.13928
16 76.81064 37.62227 9.385295
18 84.24161 41.1902 10.26256
20 90.03312 43.95864 10.94115
30 103.9081 50.54583 12.54824
40 107.083 52.04393 12.91223
];

% Hannover Inhalation plasma NMP (T, 80mg CVEN, 39mg CVEN, 9.7 mg CVEN)

H_PLAS_NMP = [3.096 0.954 3.292 0.458 3.29 0.17
6.241 1.517 6.153 0.649 6.29 0.29
7.358 0.938 7.337 0.417 7.29 0.18
8.251 0.719 8.38 0.361 8.29 0.14
10.11 0.505 10.14 0.258 10.29 0.13
24.358 0.088 24.551 0.027 24.81 0.04
48.641 0.005 47.273 0.017 NaN NaN
];

% Hannover Inhalation plasma NMP (T, 80mg CVEN1, 39mg CVEN1, 9.7 mg CVEN1)

H_PLAS_5HNMP = [3.096 1.44 3.292 0.688 3.29 0.21
6.241 2.94 6.153 1.425 6.29 0.39
7.358 3.19 7.337 1.488 7.29 0.39
8.251 3.14 8.38 1.463 8.29 0.36
10.11 2.91 10.14 1.35 10.29 0.36
24.358 0.61 24.551 0.238 NaN NaN
];

% Hannover Inhalation plasma NMP (T, 80mg AUNP, 39mg AUNP, 9.7 mg AUNP)

H_URIN_NMP = [3.096 0.23 3.292 0.132 3.29 0.08
7.358 0.67 7.337 0.339 7.29 0.16
10.11 0.86 10.14 0.512 10.29 0.2
24.358 1.03 24.551 0.565 24.81 0.26
48.641 1.07 47.273 0.599 48.37 0.26
];

% Hannover Inhalation urine 5HNMP (T, 80mg AUHP, 39mg AUHP, 9.7 mg AUHP)

H_URIN_5HNMP = [3.096 5.74 3.292 3.72 3.29 2.51
7.358 22.84 7.337 10.81 7.29 5.73

```
10.11 50.47 10.14 22.22 10.29 8.75
24.358 89.36 24.551 45.11 24.81 18.36
48.641 99.25 47.273 48.87 48.37 20.51
```

```
];
```

```
prepare @clear T CVEN CVEN1 AUNP AUHP
```

```
CONCMGM=80, start @nocallback
```

```
holdcv=[_t_cven];
```

```
holdcvhp=[_t_cven1];
```

```
holdaunp=[_t_aunp];
```

```
holdauhp=[_t_auhp];
```

```
for CONCMGM=[39 9.7]
```

```
start @nocallback
```

```
holdcv=[holdcv_cven];
```

```
holdcvhp=[holdcvhp_cven1];
```

```
holdaunp=[holdaunp_aunp];
```

```
holdauhp=[holdauhp_auhp];
```

```
end
```

```
plot(holdcv(:,1),holdcv(:,2:4), PLAS_NMP(:,1), PLAS_NMP(:,2:4),H_PLAS_NMP(:,1),
H_PLAS_NMP(:,2),H_PLAS_NMP(:,3), H_PLAS_NMP(:,4),H_PLAS_NMP(:,5), H_PLAS_NMP(:,6),'Poet 2013
Fig 4 Hannover plasma NMP.APS')
```

```
plot(holdcvhp(:,1),holdcvhp(:,2:4),PLAS_5HNMP(:,1),
PLAS_5HNMP(:,2:4),H_PLAS_5HNMP(:,1),H_PLAS_5HNMP(:,2),H_PLAS_NMP(:,3),
H_PLAS_5HNMP(:,4),H_PLAS_5HNMP(:,5), H_PLAS_5HNMP(:,6),'Poet 2013 Fig 4 Hannover plasma
5HNMP.APS')
```

```
plot(holdaunp(:,1),holdaunp(:,2:4),URIN_NMP(:,1), URIN_NMP(:,2:4),H_URIN_NMP(:,1),
H_URIN_NMP(:,2),H_URIN_NMP(:,3), H_URIN_NMP(:,4),H_URIN_NMP(:,5), H_URIN_NMP(:,6),'Poet
2013 Fig 4 Hannover urine NMP.APS')
```

```
plot(holdauhp(:,1),holdauhp(:,2:4),URIN_5HNMP(:,1), URIN_5HNMP(:,2:4),H_URIN_5HNMP(:,1),
H_URIN_5HNMP(:,2),H_URIN_5HNMP(:,3), H_URIN_5HNMP(:,4),H_URIN_5HNMP(:,5),
H_URIN_5HNMP(:,6),'Poet 2013 Fig 4 Hannover urine 5HNMP.APS')
```

POET_2013_FIG_7_PLASMA.M

human_params

P2=8; SA=7500; BWINIT=75; HT=178.5; TSTOP=72

QPC=40,QCC=23,QSKC=0.18 %Andersen et al '87 as work, CORLEY ET AL

% Poet 2013 Inhalation plasma NMP (T, 53mg CVEN, 24mg CVEN, 10mg CVEN)

PLAS_NMP = [1 0.164826 0.395742 0.874626

2	0.246282	0.591566	1.30846
4	0.344082	0.827175	1.832502
6	0.392776	0.944901	2.096089
8	0.416782	1.003176	2.228192
10	0.182521	0.439988	0.979863
12	0.090665	0.218696	0.487648
14	0.045029	0.10865	0.242425
16	0.022361	0.053964	0.120446
18	0.011104	0.026799	0.059824
20	0.005514	0.013307	0.029709
22	0.002738	0.006608	0.014753
24	0.001359	0.003281	0.007326

];

% Akesson adn Paulsson Inhalation plasma NMP (T, 80mg CVEN, 39mg CVEN, 9.7 mg CVEN)

AP_PLAS_NMP = [4 0.3 0.99 1.6

8	0.49	0.82	2.6
9	0.3	0.72	2
10	0.22	0.51	1.28
12	0.12	0.3	0.75
16	0.08	0.2	0.3
24	0.03	0.06	0.08
32	0.01	0.02	0.03
48	0.01	0.01	0.02

];

prepare @clear T CVEN CVEN1 AUNP AUHP

CONCMGM=53; start @nocallback

holdcv=[_t_cven];

holdcvhp=[_t_cven1];

holdaunp=[_t_aunp];

holdauhp=[_t_auhp];

for CONCMGM=[24 10]

start @nocallback

holdcv=[holdcv_cven];

holdcvhp=[holdcvhp_cven1];

holdaunp=[holdaunp_aunp];

holdauhp=[holdauhp_auhp];

end

```
plot(holdcv(:,1),holdcv(:,2:4),PLAS_NMP(:,1),PLAS_NMP(:,[4 3 2]),AP_PLAS_NMP(:,1), AP_PLAS_NMP(:,[4  
3 2]), 'Poet 2013 Fig 5 Akesson and Paulsson plasma')  
%plot(holdcvhp(:,1),holdcvhp(:,2:4),'FIGAKinhalcvhp.APS')  
%plot(holdauhp(:,1),holdauhp(:,2:4), 'FIGAKinhalaunp.APS')  
%plot(holdaunp(:,1),holdaunp(:,2:4),'FIGAKinhalaunp.APS')
```

POET_2013_FIG 8AB_PLASMA_&_URINE.M

human_params % Uncommented to assure consistent parameters; Paul Schlosser, U.S. EPA (PS), 5-17-2013

SAL=5; SAV=1e-4; BWINIT=67.5; HT=160.0; %Wikipedia - German men weight 82.4 kg, women weigh 67.5kg)

CONCL=1045000; VLIQ=0.0003; BRUSH=1; TSTOP=48; P2=6; WKDAYS=1; CINTC=0.1;

%FAD=1 %most was recovered on pad - 18.6 is "lost" to system.

% FAD set in human_params.m, PS 5-17-13

%PV=0 % Intrinsic property for skin-air transport should not change from that set in human_params.m ...

% Since air concentration(s) are set to zero, this should not need to be zeroed

here; PS 5-17-13

% Allowing PV=32 (default value) reduces predicted NMP and 5-HNMP by ~ 6% vs. PV =

0; PS 5-17-13

% PVL= 2.9e-003 % If PV=32, this value of PVL gives nearly the same 'cvhp' and 'auhp' simulations; PS 5-17-13

% Poet 2013 Dermal sims plasma NMP: 0.3 ml NMP applied)

PLAS_NMP = [2 0.2704 0.2170

4 0.6709 0.5418

6 1.050 0.8547

8 1.1445 0.9437

10 1.0497 0.8795

12 0.8898 0.7581

14 0.7220 0.6256

16 0.5704 0.5026

18 0.5635 0.4968

20 0.3401 0.3095

22 0.2590 0.2395

24 0.1962 0.1843

30 0.0837 0.0822

40 0.0197 0.0208

];

% Poet 2013 Dermal sims urine NMP: 0.3 ml NMP applied)

URIN_NMP = [2 0.4701 0.4381

4 2.4293 2.2716

6 6.0414 5.6806

8 10.7190 10.1404

10 15.3381 14.6079

12 19.4052 18.6049

14 22.7817 21.9778

16 NaN 24.98211

18 27.6136 26.9195

20 29.2560 28.6418

22 30.5132 29.9812

24 31.4690 31.0154

30 33.1474 32.8825

40 34.0853 33.9834

];

% Akesson 2004 Dermal plasma NMP: 0.3 ml NMP applied)

A_PLAS_NMP = [1.01 0.22 0.07

1.94 0.66 0.49

4.06 1.15 0.85

5.83 1.01 1.03

7.95 1.01 0.97

12.1 0.58 0.73

24 0.18 0.14

30.1 0.07 0.04

47.9 0.02 0.01

];

% Akesson 2004 Dermal urine NMP: 0.3 ml NMP applied)

A_URIN_NMP = [1 0.610509 0.451446

3 5.998437 4.368267

5 13.64819 9.921695

7 21.16922 16.61523

9 26.72265 21.70894

11 30.84175 24.85343

14 36.38598 30.03908

20 41.33442 34.87718

27 42.67313 36.24163

39 42.87835 36.44023

];

prepare @clear T CVEN1 AUHP

% women

start @nocallback

holdcvhp=[_t_cven1];

holdauhp=[_t_auhp];

BWINIT=82.4; % men

start @nocallback

holdcvhp=[holdcvhp_cven1];

holdauhp=[holdauhp_auhp];

plot(holdcvhp(:,1),holdcvhp(:,2:3),PLAS_NMP(:,1),

PLAS_NMP(:,2:3),A_PLAS_NMP(:,1),A_PLAS_NMP(:,2:3), 'Poet 2013 Fig 8 plasma.APS')

plot(holdauhp(:,1),holdauhp(:,2:3),URIN_NMP(:,1),

URIN_NMP(:,2:3),A_URIN_NMP(:,1),A_URIN_NMP(:,2:3), 'Poet 2013 Fig 8 urine.APS')

%ADVL

%AUNP

POET_2013_FIG_9_PLASMA.M

human_params % Uncommented to assure consistent parameters; Paul Schlosser, U.S. EPA (PS), 5-17-2013

DOSE=0,PDOSE=0,TCHNG=4,DOSINTERVAL=2.93,IVDOSE=0
CONCMGM=0,SAL=5, SAV=1e-4

CONCL=1045000,VLIQ=0.0003

BWINIT=79, HT=160, TSTOP=48,TCHNG=6, BRUSH=1, P2=6, ON3=0

%FAD=1 %most was recovered on pad - 18.6 is "lost" to system.

% FAD set in human_params.m, PS 5-17-13

PV=0 % Intrinsic property for skin-air transport should not change from that set in human_params.m ...

% Since air concentration(s) are set to zero, this should not need to be zeroed
here; PS 5-17-13

% Allowing PV=32 (default value) reduces predicted NMP and 5-HNMP by ~ 6% vs. PV = 0; PS 5-17-13

% PVL= 2.9e-003 % If PV=32, this value of PVL gives nearly the same 'cvhp' and 'auhp' simulations; PS 5-17-13

% Poet 2013 Dermal sims plasma NMP: 0.3 ml NMP applied)

PLAS_NMP = [2 0.2527079

4	0.4365436
6	0.512324
8	0.338109
10	0.1865714
12	0.1029197
14	0.05676336
16	0.03130336
18	0.01726188
20	0.009518544
22	0.00524862
24	0.002894112
30	0.000485194
40	0.000024731

];

% Akesson and Paulsson 1997 inhalation data

AP_PLAS_NMP = [4 0.3

8	0.49
9	0.3
10	0.22
12	0.12
16	0.08
24	0.03
32	0.01
48	0.01

];

CINTC=0.1; prepare @clear T CVEN

!!START /NC

holdcvnp=[_t _cven];

plot(holdcvnp(:,1),holdcvnp(:,2),PLAS_NMP(:,1),PLAS_NMP(:,2),AP_PLAS_NMP(:,1),AP_PLAS_NMP(:,2),
'Poet 2013 Fig 9 plasma.APS')

APPENDIX B. Corrections and changes in the PBPK models for *N*-Methylpyrrolidone as described by Poet (2013) (revised by T. Poet from that described in Poet et al., 2010)

Rat PBPK Model

Oral Dosing

While oral exposure is not a route of con

Exposure control

Because both Becci et al. (1982) and Saillenfait et al. (2002) explicitly stated that the animal BWs were measured every 3rd day of gestation, and the dermal/oral doses were adjusted accordingly on those days (as BW increases during pregnancy), corresponding conditional (if/then) statements were added to the 'GAVD' and 'REAPPLY' discrete blocks, to re-calculate the doses on those days.

The code for the dermal discrete blocks follows. ASK0 is the absolute amount applied on each day; DSK is the dose/kg BW. Because Becci et al. (1982) rubbed the material into the skin, it is assumed to be added directly into the skin compartment (ASK), rather than as a liquid on top. Hence the dose is given as an addition of ASK0 (mg/day applied) to ASK.

```
DISCRETE SKWASH      ! PMS, 8-14-13
  ASK = 0.0           ! Assume skin washing in Becci et al. (1982) removes all NMP from skin
  if (DAYS.LT.15.0) SCHEDULE REAPPLY.AT.(T+DOSEINTERVAL-TWASH)
END
DISCRETE REAPPLY      ! PMS, 8-14-13
  IF (ROUND(DAYS).EQ.9.0) ASKO=DSK*BW
  IF (ROUND(DAYS).EQ.12.0) ASKO=DSK*BW
  IF (ROUND(DAYS).EQ.15.0) ASKO=DSK*BW
  ASK = ASK + ASKO
  SCHEDULE SKWASH.AT.(T+TWASH)
END
```

Also, because Becci et al. (1982) washed the skin area exposed to dermal application at the end of a set time interval, a "SKWASH" discrete block was introduced at which time the amount in that patch of skin was assumed to be momentarily reduced to zero. During periods of dermal application, transport from the liquid to the skin was turned on using the pulse function, DZONE. After removal of the liquid it was assumed that NMP in the skin patch could volatilize into the otherwise clean air, with the rate defined by the same permeability constants, but using the skin:air partition coefficient.

The rate of transfer to/from the skin area is then defined by:

```
RADL=(KPL*SA/1000.0)*((CSURF-(CSK/PSKL))*DZONE - (1.0-DZONE)*(CSK/PSKA))
! 2ND term, (1.0-DZONE)*(CSK/PSKA), allows for evaporative loss when DZONE=0
```

Finally, a constant, CONCMGS, was introduced so that the air concentration could be set directly in mg/m³. This is converted to the concentration in mg/L (CONCMG) in the code and added to the

inhalation exposure, turned on and off using the switch, CIZONE, which is turned on and off using SCHEDULE/DISCRETE statements:

CI = CCH*PULSE(0., DOSEINTERVAL,TCHNG) + CIZONE*CONCMG ! MG/L ! Added
CIZONE*CONCMG, PMS, 8-13-13

Skin compartment

Corrections to the mass balance equations for the rat skin are as indicated in the commented code copied below. It includes the initial condition, ASK0, for the initial dermal application, but is otherwise now the standard format for PBPK models. As received the code had multiplied CSK rather than CSKV (skin venous blood concentration) by the blood flow (QSKN) for the rate of efflux in blood, and had not separately calculated CSKV.

RASK = QSKN*(CA - CSKV) + RADL ! NOW MINUS CSKV, NOT CSK; PMS 8-21-13
ASK = INTEG(RASK,ASK0) ! Initial value, ASK0, added for Becci et al. (1982) exposures; pms
8-14-13
CSK = ASK/VSK !'NMP IN SKIN, MG/L'
CSKV = CSK/PSKB ! NMP IN VENOUS BLOOD, PMS 8-22-13

The corresponding flow term for transfer from the skin to the mixed venous blood compartment was also corrected (ie, to use CVSK instead of CSK).

While these changes to the skin compartment equations initially degraded the fits to the dermal exposure considerably, it also appeared that the associated partition coefficients were not consistent with the measured values reported by Poet et al. (2010), Table 5. They were recalculated as follows:

Skin:liquid, PSKL = 0.42: value as measured for skin:saline, vs. 450

Skin:blood, PSKB = 0.12: (skin:saline)/(blood:saline)

Skin:air, PSKA = 55: (skin:saline)*(blood:air)/(blood:saline) = (skin:blood)*(blood:air)

Blood flows

Since the placenta is a separate compartment for the 5HNMP compartment, its blood-flow and volume were removed from the sums used for the 'rest of body' for 5HNMP. Also, the term for blood flow from the placenta was added to the mixed-venous blood mass balance for 5HNMP.

To assure flow mass balance, instead of calculating cardiac output (QC) as an initial amount plus the change from initial for each compartment, it was just calculated as the sum over all the compartments:

! QC = QCINIT + (QFAT - QFATI) + (QMAM - QMAMI) + QPLA + (QUTR - QUTRI)
QC = QFAT+QLIV+QSLW+QRAP+QSKN+QMAM+QPLA+QUTR ! pms, 8-13-13

Parameter Consolidation

In the provided files, some physiological and chemical-specific parameter were set in separate scripts; e.g., skin transport parameters in the dermal exposure scripts. This approach creates the potential for inconsistent parameters between different exposure simulations. Therefore all parameters are now set in the ratparam.m script except those which are experimental control variables (eg., air concentration,

duration of exposure). The final set of parameters used and any inconsistencies with previous values in ratparam.m that may have differed are noted in that script.

Human PBPK Model

Exposure and Timing Control

A table function, RESLVL, was added as a place-holder for reading in defined (residential) inhalation exposure time-courses; specifically from U.S. EPA exposure assessment modeling.

A constant, GDstart, the day of gestation on which the simulation starts, and a variable Gtime, the hours into gestation, were added to facilitate separating exposure control from gestation timing

A second set of DISCRETE/SCHEDULE blocks were added to allow for split exposure scenarios (morning/afternoon worker exposure; dual-episode residential exposures).

DZONE, set in the DISCRETE/SCHEDULE blocks, controls the time within a day when discontinuous exposure occurs. Czone is the product of DZONE and a pulse function used to control for days/week exposure in workplace scenarios:

Czone = pulse(0.0,fullweek,hrsweek)*DZONE ! pms 8-20-13
! for a 5 day/wk exposure, use fullweek=7*24, hrsweek=5*24 (Dayswk=5)
! for a single day, fullweek=1e16, hrsweek=24 (Dayswk=1)

A binary constant, BRUSH, was added to set when dermal contact with liquid occurs. The rate for delivery from a liquid film to the 'SKL' skin compartment (also see further below) is then defined by:

$$RASL=(PVL*SAL/1000.0)*(CSURF-(CSKL/PSKL))*Czone*BRUSH$$

A constant SRATE was added for the net rate of delivery by liquid droplets to the skin for workplace spray applications. This is a net rate delivered into the skin compartment, rather than a liquid layer on the surface, assuming that the exposure modeling already accounts for material that may be temporarily deposited on the surface but not absorbed. (Absorption from a liquid layer of a defined (possibly changing) concentration was retained for other exposure scenarios, including residential.) When spray delivery SRATE is non-zero, concentration-driven transport from liquid or vapor is turned off for the spray/liquid exposed skin. The equations for transfer of vapor (air concentration = CI) to the SKL compartment, which occurs during periods with no liquid/spray contact, **and/or** spray absorption for the SKL compartment are then:

Sdeliv = SRATE*Czone ! Constant-rate spray delivery; pms 8-20-13
! Spray-dermal exposures, assumed simultaneous with inhalation (unless FRACIN = 0)
RADVL = (PV*SAL/1000.0)*(CI - (CSKL/PSKA))*(1.0-Czone*BRUSH)*(Sdeliv.eq.0.0) + Sdeliv
! RADVL allows absorption/desorption from air when there is NOT spray or
! brushing dermal exposure, when both sdeliv and czone are zero; pms 8-20-13

Skin compartment

As for the rat, and noted in the main report, corrections were made to the human skin transport and PK (equations not shown here, but same as for rat). The partition coefficients were also recalculated as was done for the rat, with rat parameters for skin:saline and blood:air, but human blood:saline.

The original skin compartment which is coded to include uptake from liquid-dermal contact was renamed by adding "L" to the end, SK → SKL, and second skin compartment to account for concurrent vapor-skin uptake, SKV, was added. This was done because when the human model was calibrated for inhalation exposure, an exposed skin surface area of 6700 cm² was used. When this surface area is reduced to ~ 0, predicted blood levels of NMP shown in the upper panel of Figure 4 in the QA report are reduced ~ 45%. Thus vapor uptake through the skin is a significant component of inhalation exposure and there is no reason to assume, *a priori*, that this uptake does not occur through a similar area of exposed skin during workplace and residential exposures, except for any area that would have liquid contact or otherwise be occluded (e.g., by wearing rubber gloves). So the SKV compartment allows for simultaneous absorption of vapor through skin that does not have liquid contact, and from areas of skin with liquid contact. The surface area of SKV and SKL are SAV and SAL, respectively, and can be set for different exposure scenarios. For EPA simulations, SAV was reduced from 6700 cm² by the area assumed to have liquid contact or covered by gloves for those scenarios. To evaluate the impact of this assumption for workplace exposure simulations were also conducted with SAV set to 0.01 cm² for a low rate of dermal delivery (600 mg/day).

Tissue and blood-flow mass balances

The model had been previously coded with an alveolar blood compartment (ALV), but this was commented out by the author in the DYNAMIC section. Therefore this volume fraction should not be subtracted when calculating the slowly-perfused volume. The fraction of blood-flow to slowly perfused tissue was updated to also account for the SKV compartment; on the other hand a separate skin compartment is not used for 5HNMP, so the skin blood flow is NOT subtracted for the metabolite-slowly-perfused compartment (SLW5). These have all been corrected.

QSKCC (original fractional flow to the skin) had been subtracted twice, both in calculating QSLWC and then in the calculation of QSLW. The 2nd subtracted created a mass balance error and hence was removed. On the other hand, placental blood flow is now subtracted, so the total flow to slowly-perfused continues to total cardiac output minus all other tissue/group flows.

For tissues that change with gestation day, the initial values were corrected to match the calculation in the DYNAMIC section, which would apply at the first time-step.

In the dynamic section, the calculation of QC was corrected to include the *increase* in placental flow (QPLA – QPLAI) rather than the total placental flow (QPLA), since QCINIT includes QPLAI. QSLW5 and VSLW5 (5HNMP slow compartment flow and volume) are now calculated in the DYNAMIC section by subtraction.

Oral absorption parameters and equations

The oral absorption rate as a function of the amount in the stomach lumen compartment, AO, had been erroneously written as, $RAO = KAS * FRACOR * AO$, with the initial amount in the compartment set to be

the total administered dose, ODOSE. Since there is no other route of clearance from the stomach lumen compartment, this approach only reduces the effective absorption rate constant from KAS to $KAS \cdot \text{FRACOR}$ without reducing the total amount absorbed. Using the code as provided and the parameters for absorption listed in Poet et al. (2010) gives a significant overprediction of the plasma NMP levels, not consistent with the simulations shown in Fig. 5 of Poet et al. (2010), which appear to fit those data well. Therefore the code was corrected to make

$$\text{ODOSE} = \text{FRACOR} \cdot \text{DOSE} \cdot \text{BWINIT}$$

(instead of $\text{DOSE} \cdot \text{BWINIT}$) and

$$\text{RAO} = \text{KAS} \cdot \text{AO}.$$

When this was done the AUC for plasma NMP appeared to be approximately correct, but the initial rise vs. time was faster and the peak occurred earlier than shown in Fig. 5 of Poet et al. (2010). When KAS was then reduced by FRACOR (68%), the model simulations shown in the preface for this report were obtained. The simulations for plasma NMP are quite close to those shown in Figure 5 of Poet et al. (2010) and fit the data fairly well. Therefore it is assumed that the results of Poet et al. (2010) included the multiplication by FRACOR in computing RAO, but also reduced the oral dose by FRACOR. The U.S. EA version uses the corrected equations shown just above, to deconvolute the two parameters (FRACOR and KAS) and allow DOSE to simply be set to the applied dose.

Parameter Consolidation

As for the rat model, the human model physiological and biochemical parameters are now all set in a single script, human_params.m. Only constants which define specific exposure scenarios (include skin areas exposed) are defined in the specific simulation scripts.